Durable Control of Viral Rebound in Humanized Mice by ABX464 Targeting Rev Functions

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J. TAZI received research grants awarded to his institution from ABIVAX, has served as consultant to ABIVAX and owns stock in ABIVAX
>90% of intron-containing genes are alternatively spliced

Tissue-specific regulation for >50% of splicing events

PremRNA splicing a major contributor of protein diversity
How cells get the message: dynamic assembly and function of mRNA–protein complexes
RNA processing plays a large role in HIV replication
HIV Infection in Target T cells

**Latent infection**
- Docking
- Fusion
- Reverse transcription
- Integration
- Chromosomal DNA
- Provirus

**Active infection**
- 1. Transcription of proviral DNA
- 2. Synthesis of viral components
- 3. Assembly of viruses
- 4. Budding of viruses from the host cell

**Steps**
1. Transcription of proviral DNA
2. Synthesis of viral components
3. Assembly of viruses
4. Budding of viruses from the host cell
Viral proteins

TREX-dependent export

Fully spliced mRNAs

Intron containing mRNAs

Rev/CRM1-dependent export

Transcription, RNP assembly, RNA processing

5’LTR

Gag

Pol

Vif

Tat

Rev

Vpr

Vpu

Env

Nef

3’LTR

TAR

RRE

CBC

A(An)A

SR

hnRNP

TREX

Rev

New viruses
• Cellular quality control mechanisms retain and degrade unspliced or partially spliced mRNA

• The cellular quality control involves TREX and the Cap Binding Complex that facilitates Nuclear Export of both cellular and fully spliced viral RNA

• Rev protein allows the unspliced viral RNAs to escape the cellular quality control and to be exported by a mechanism dependent on CRM1 and the Cap Binding Complex

• Given that Rev protein is produced from fully spliced RNA, either inhibition or activation of viral RNA splicing will impede viral replication in infected cells
Small-Molecule Inhibition of HIV pre-mRNA Splicing as a Novel Antiretroviral Therapy to Overcome Drug Resistance

Bakkour et al, PloS Path, 2007
cellular splicing is unaffected by the ABX464
Rev protein specifies the viral RNA export pathway through interaction with the Cap Binding complex.
Promoter

SD1

ψ

RRE

SA7

Poly A

MS2-GFP

INTRON: 4.2 Kb

2.1 Kb → 128xMS: 3Kb → 1.6 Kb

INTRON: 4.2 Kb
ABX464 prevents Rev-mediated export of unspliced viral RNA
ABX464 interacts with the Cap Binding Complex
Rev Tat

New viruses

Viral proteins

Rev/CRM1-dependent export

TREX-dependent export

5'LTR

Gag Pol

Vif Rev

Vpr

Vpu

Env

3'LTR

TAR

RRE

A(An)A

CBC

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SR

CBC

Fully spliced mRNAs

Intron-containing mRNAs

Transcription, RNP assembly, RNA processing

ABX464

Rev-dependent export

TREX-dependent export
Efficient inhibition of various HIV subtypes in PBMCs and macrophages by ABX464

<table>
<thead>
<tr>
<th>HIV-1 strains</th>
<th>% of inhibition with ABX464</th>
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<td>HIV-1 B subtype</td>
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<tr>
<td>Ad8</td>
<td>71 ± 4</td>
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<td>AdaM</td>
<td>99 ± 1</td>
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<tr>
<td>Isolate B</td>
<td>83 ± 8</td>
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<td>HIV-1 C subtype</td>
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<tr>
<td>Isolate C</td>
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<td>HIV-1 recombinants</td>
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<td>CRF01</td>
<td>82 ± 11</td>
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<td>CRF02</td>
<td>86 ± 3</td>
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<td>CRF06</td>
<td>80 ± 5</td>
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</table>
ABX464 inhibits 3TC resistant strains

Efficacy on NL4.3 resistant viruses

![Graph showing the efficacy of ABX464 on different strains of NL4.3 resistant HIV viruses. The graph compares the HIV RT activity (cpm) of Control, ABX464, and 3TC for strains K103N, K65R, and M184V.]
### Table 1: Amino Acid Changes

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<td>CODON REF/ALT</td>
<td>CAT/CCT</td>
<td>GAG/GTG</td>
<td>TAT/TAC</td>
<td>GTA/GGT</td>
<td>ATG(start)/CTG</td>
<td>GCA/GAG-GGC</td>
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<td>Env: ATG/ATA</td>
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<td>AA Ref/Alt</td>
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<td>M/L</td>
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<td>(8) D4 treated with ABX-464</td>
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</table>

### Diagram 1: Protein Structures

- **GAG polypeptide**
- **POI protein**
- **tat**
- **V3 region**
- **polyA Signal**

### Diagram 2: Protein Structures

- **GAG polypeptide**
- **POI protein**
- **tat**
- **V3 region**
- **polyA Signal**

### Notes

- **Ref/Alt**: Reference/Alternative
- **AA**: Amino Acid
- **POS**: Position
- **ACT**: Action
- **T/C**: Transition/Transversion

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- **5pLTR**: 5' Long Terminal Repeat
- **3pLTR**: 3' Long Terminal Repeat
- **Env**: Envelope
- **Vpu**: Viral Protein U5
- **Nef**: Nuclear Envelope Factor
- **V3**: V3 Region
- **Ref**: Reference
### HIV drug resistance in vitro*
(6-month follow-up)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time to HIV resistance (weeks)</th>
<th>HIV Mutants</th>
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<tr>
<td>3TC</td>
<td>4</td>
<td>M184I/V</td>
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<tr>
<td>Tenofovir</td>
<td>12</td>
<td>K65R</td>
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<td>Nevirapine</td>
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<td>K103N, Y181C</td>
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<td>Efavirenz</td>
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<td>K103N, Y181C</td>
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<tr>
<td>ABX464</td>
<td>No HIV resistance</td>
<td>-</td>
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</table>
Efficacy of ABX464 in humanized mouse models

Days post-infection/treatment

RNA copies/mL

0 5 10 15 20

1×10^0  1×10^1  1×10^2  1×10^3  1×10^4  1×10^5  1×10^6

mock ABX464

51.3% 51.3% 90.1%
45.2% 43.3%
8.7% 52.8%

Not infected Mock ABX464

Gavage

HIV RNA [copies/mL]

0 50 100 150

days post infection

1×10^0  1×10^1  1×10^2  1×10^3  1×10^4  1×10^5  1×10^6


HAART

HIV RNA [copies/mL]

0 50 100 150

days post infection

1×10^0  1×10^1  1×10^2  1×10^3  1×10^4  1×10^5  1×10^6

345. 322. 348. 355. 312. 356.
ABX464 is an anti-HIV drug able to suppress viral load sustainably after treatment arrest.
ABX464 represents a novel class of anti-HIV molecules with unique properties.

- ABX464 interferes with Rev-mediated RNA biogenesis
- ABX464 does not select for HIV specific mutations and it is not genotoxic
- ABX464 has a long lasting effect in humanized mice

- **Phase I data showed excellent safety and PK profile**
Paved the way for on-going phase Iia

- **Phase Ila dose ranging study initiated:**
  80 naïve HIV patients
  10 groups of 8 patients Escalating Doses: 25, 50, 75, 100 and 150 mg per day
Acknowledgments
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