The Use of Antivirals to Rapidly Contain Outbreaks of the Classical Swine Fever Virus

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Rega Institute, KULeuven, Leuven Belgium

Novel HCV Inhibitors
Selective Inhibitors of HCV Replication that Target NS Proteins
The NS2 cysteine protease

NS2/3 cleavage is essential for replication and assembly

The HCV NS3 serine protease

N-terminal domain: a serine protease in the presence of the NS4A cofactor protein

C-terminal domain: RNA helicase

De Francesco et al. 2001

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
NS3 protease product based inhibitors

carboxy-terminal hexapeptide products as an active-site affinity anchor
Proof of concept with BILN-2061 (Ciluprevir)


Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Telaprevir monotherapy

Reesink et al., Hepatology (2005) 42 : 234A

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
The Major VX-950 and BILN2061 Resistance Mutations Do Not Cause Cross-resistance


Others : GS9256 - BI201335 - BMS-650032 - RG7227 - IDX320 - ABT-450

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
# Resistance mutations selected by protease inhibitors

<table>
<thead>
<tr>
<th></th>
<th>T54T-V</th>
<th>R155Q</th>
<th>A156S/T</th>
<th>D168V/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir (VX950)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Boceprevir</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>TMC435350</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ITMN-191</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ciluprevir (BILN-2061)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Sheldon et al., (2007) Expert Opinion Anti-Infectives

*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*
The NS3 Helicase as an Antiviral Target


Dr. A. Brancale (Cardiff)
Mutations located where extensive interactions with NS4A exist.

No cross resistance with (other) NS3 and with NS5B inhibitors

NS4B as an Antiviral Target

NS4B : difficult to express membrane protein that is believed to interact with viral RNA

Binding assay of 3’ terminal –ssRNA (labelled) to <<< quantity of NS4B protein

library screen

Clemizole

Einav et al., Nat. Biotech.2008

NS5A as an Antiviral Target

Domain I (without α-helix) crystallizes as a colinear homodimer (Tellinghuize et al., Love et al.).

Membrane-associated phosphoprotein involved in replication and virus production. No enzymatic activity associated

**AA 1 to 30**: membrane anchor, directing NS5A to the ER

**AA 5 to 25**: amphipathic α-helix with a lipid bilayer-associated hydrophobic face and a solvent-exposed polar face

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
NS5A inhibitor (BMS-790052)

- Not cross resistant with other HCV inhibitors
- Mutations in N-terminus of domain 1.
- If transitioning between dimer configurations is important for HCV replication BMS-790052 may possibly influence this transition.
- May possibly prevent formation of a multiprotein complex on ER membrane.
- Blocks the hyperphosphorylation of NS5A (essential role in the viral life cycle).
- Causes redistribution of NS5A


HCV replicon genotype 1a, H77
HCV replicon genotype 1b, Con1
HCV replicon genotype 2a, JFH
HCV replicon genotype 2a, JFH*
HCV replicon genotype 3a*
HCV replicon genotype 4a*
HCV replicon genotype 5a*
Infectious HCV, genotype 2a, JFH

50 ± 13 pM
9 ± 4 pM
71 ± 17 pM
103 ± 36 pM
146 ± 34 pM
12 ± 4 pM
33 ± 10 pM
28 ± 24 pM
NS5A inhibitor (BMS-790052)

Scheel et al., Hepatology, 2010

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
NS5A inhibitor (BMS-790052)

Mean change in HCV RNA following a single oral dose (phase I study)

Phase II studies combining BMS-790052 with the NS3 protease inhibitor BMS-650032 are ongoing.

This combination (alone or with PEGIFN and RBV) results in undetectable HCV RNA through 12 weeks of therapy in HCV genotype 1 null responders

The NS5B RNA dependent RNA polymerase
Nucleoside inhibitors

Valopicitabine (NM-283)

R7128: di-isobutyl ester prodrug of PSI-6130

7-Deaza-2'-C-methyl-adenosine

MK-0608

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Non- Nucleoside inhibitors Benzimidazole/indoles

Intramolecular contacts between the thumb and the finger domain may force the enzyme into an ‘open’, inactive conformation.
Non-Nucleoside inhibitors: Thiophene carboxylic acid / Pyranoindole / Dihydropyranone

VCH-916, PF-868554/Filibuvir,

Met423, Leu419
Non- Nucleoside inhibitors Benzothiadiazine/Acylpyrrolidines

ABT-333
ANA598,
Non-Nucleoside inhibitors Benzofuran

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Combinations of Non Nuc NS5B Inhibitors Delay or Prevent Resistance Development

HCV-796 + JT-16

HCV-796

0 160 nM 400 nM 2 μM

0

2.9 μM

7.25 μM

C316Y, C445F
2211 fold resistance against HCV-796

T389A/T, C445F/C, P495L/P
8 fold resistance against JT-16

Delang et al., 2011 J. Hepatol, in press

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
## Double and triple resistant variants

<table>
<thead>
<tr>
<th>Cell type</th>
<th>JT-16</th>
<th>TCA</th>
<th>HCV-796</th>
<th>GSK-4</th>
<th>2’-C-MC</th>
<th>VX-950</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NNI, thumb domain 1</td>
<td>NNI, thumb domain 2</td>
<td>NNI, palm domain 2</td>
<td>NNI, palm domain 1</td>
<td>NI</td>
<td>P1</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>TCA&lt;sup&gt;res&lt;/sup&gt; + HCV-796&lt;sup&gt;res&lt;/sup&gt;</th>
<th>TCA&lt;sup&gt;res&lt;/sup&gt; + HCV-796&lt;sup&gt;res&lt;/sup&gt; + JT-16&lt;sup&gt;res&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA&lt;sup&gt;res&lt;/sup&gt; + HCV-796&lt;sup&gt;res&lt;/sup&gt;</td>
<td>1.8 ± 0.2 (1.2)</td>
<td>13 ± 1.4 (8.7)</td>
</tr>
<tr>
<td>TCA&lt;sup&gt;res&lt;/sup&gt; + HCV-796&lt;sup&gt;res&lt;/sup&gt; + JT-16&lt;sup&gt;res&lt;/sup&gt;</td>
<td>16 ± 3.1 (164)</td>
<td>30 ± 0.3 (288)</td>
</tr>
</tbody>
</table>

Delang et al. , J. Hepatol, in press (2011)
Discovery of the imidazopyridine GS-9190 (Tegobuvir)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPIP</td>
<td><img src="image1" alt="Structure" /></td>
</tr>
<tr>
<td>Compound 1</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>Compound 2</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
<tr>
<td>Compound 3</td>
<td><img src="image4" alt="Structure" /></td>
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<tr>
<td>Compound 4</td>
<td><img src="image5" alt="Structure" /></td>
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<tr>
<td>GS-327073</td>
<td><img src="image6" alt="Structure" /></td>
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</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC_{50} HCV</th>
<th>CC_{50} HCV</th>
<th>EC_{50} BVDV</th>
<th>CC_{50} BVDV</th>
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</thead>
<tbody>
<tr>
<td>BPIP</td>
<td>&gt;50</td>
<td>80 ± 11</td>
<td>0.07 ± 0.02</td>
<td>83 ± 20</td>
</tr>
<tr>
<td>Compound 1</td>
<td>3.0 ± 1.6</td>
<td>136 ± 42</td>
<td>0.12 ± 0.01</td>
<td>&gt;33</td>
</tr>
<tr>
<td>Compound 2</td>
<td>0.6 ± 0.1</td>
<td>&gt;55</td>
<td>0.24 ± 0.12</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Compound 3</td>
<td>0.2 ± 0.1</td>
<td>&gt;119</td>
<td>0.25 ± 0.09</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Compound 4</td>
<td>0.1 ± 0.01</td>
<td>108</td>
<td>0.72 ± 0.19</td>
<td>&gt;100</td>
</tr>
<tr>
<td>GS-327073</td>
<td>0.004 ± 0.002</td>
<td>≥ 19</td>
<td>1.4 ± 0.96</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>


GS-9190 (Tegobuvir)
HCV : 1nM / BVDV > 50µM

~ 1700 molecules
GS-9190 (Tegobuvir) targets the HCV RdRp with a unique mechanism

Beta hairpin loop involved in primer independent initiation of RNA replication.

Partially cross resistant with benzofurans

Compound does not inhibit the purified RdRp.
**Tegobuvir Phase IIa study (196-0112)**

Zeuzem et al., 61st AASLD (The Liver Meeting, Nov. 2010) Boston.

<table>
<thead>
<tr>
<th>Treatment-naive adults with chronic HCV genotype 1 (28-days treatment course)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GS-9190 (40 mg twice daily)</strong></td>
</tr>
<tr>
<td><strong>GS-9256 (75 mg twice daily)</strong></td>
</tr>
<tr>
<td><strong>GS-9190 (40 mg twice daily)</strong></td>
</tr>
<tr>
<td><strong>GS-9256 (75 mg twice daily)</strong></td>
</tr>
<tr>
<td><strong>RBV (500 - 600 mg twice daily)</strong></td>
</tr>
<tr>
<td><strong>GS-9190 (40 mg twice daily)</strong></td>
</tr>
<tr>
<td><strong>GS-9256 (75 mg twice daily)</strong></td>
</tr>
<tr>
<td><strong>RBV (500 - 600 mg twice daily)</strong></td>
</tr>
<tr>
<td><strong>Peg-IFN (180 µg, inj. once/week)</strong></td>
</tr>
<tr>
<td>**14/14 patients : HCV RNA &lt; 25 IU/mL) at day 28. Median maximal decline from baseline in HCV RNA 5.7 log10 IU/mL</td>
</tr>
<tr>
<td><strong>13/14 patients : undetectable viral levels (HCV RNA &lt; 10 IU/mL) at day 28. No virologic breakthroughs</strong></td>
</tr>
</tbody>
</table>
Tegobuvir + Telaprevir

3 day antiviral combination assay

Clearance rebound assay

Vliegen et al., J. Hepatol. 2009

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Triple combinations

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Combinations

Some combinations that are in phase II

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS9256 (NS3/4A inhibitor) and GS9190 (non-nuc polymerase inhibitor)</td>
<td>Gilead [21]</td>
</tr>
<tr>
<td>BI201335 (NS3/4A inhibitor) and BI297127 (non-nuc polymerase inhibitor)</td>
<td>Boehringer [22]</td>
</tr>
<tr>
<td>BMS-650032 (NS3/4A inhibitor) and BMS-790052 (NS5a inhibitor)</td>
<td>BMS [20]</td>
</tr>
<tr>
<td>Telaprevir (NS3/4A inhibitor) with VX-222 (non-nuc polymerase inhibitor)</td>
<td>Vertex</td>
</tr>
<tr>
<td>RG7227 (NS3/4A inhibitor)/Ritonovir and RG7128 (Nuc polymerase inhibitor)</td>
<td>Roche</td>
</tr>
<tr>
<td>IDX320 (NS3/4A inhibitor) and IDX184 (Nuc polymerase inhibitor)</td>
<td>Idenix</td>
</tr>
<tr>
<td>ABT-450 (NS3/4A inhibitor)/Ritonovir and ABT-072 (non-nuc polymerase inhibitor)</td>
<td>Abbott</td>
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</tbody>
</table>
Alisporivir (Debio-025) a cyclophylin binding HCV inhibitor

<table>
<thead>
<tr>
<th>Name</th>
<th>Pos3</th>
<th>N4</th>
<th>Pos4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA</td>
<td>H</td>
<td>Me</td>
<td>Leu</td>
</tr>
<tr>
<td>DEBIO-025</td>
<td>Ala</td>
<td>Et</td>
<td>Val</td>
</tr>
</tbody>
</table>

Watashi et al., BBRC (2003)
Paeshuyse et al., Hepatology (2006)
## Alisporivir is not cross-resistant with other HCV inhibitors

<table>
<thead>
<tr>
<th>drug</th>
<th>WT</th>
<th>Alisporivir&lt;sub&gt;res&lt;/sub&gt;</th>
<th>CsA&lt;sub&gt;res&lt;/sub&gt;</th>
<th>2CMC&lt;sub&gt;res&lt;/sub&gt;</th>
<th>R1479&lt;sub&gt;res&lt;/sub&gt;</th>
<th>BILN 2061&lt;sub&gt;res&lt;/sub&gt;</th>
<th>VX-950&lt;sub&gt;res&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alisp.</td>
<td>0.04 ± 0.03</td>
<td>≥1.95</td>
<td>0.23 ± 0.17</td>
<td>0.11 ± 0.27</td>
<td>0.12 ± 0.01</td>
<td>0.1 ± 0.003</td>
<td>0.09 ± 0.01</td>
</tr>
<tr>
<td>CsA</td>
<td>0.29 ± 0.05</td>
<td>4.55 ± 3.98</td>
<td>3.82 ± 1.00</td>
<td>0.21 ± 0.04</td>
<td>0.26 ± 0.05</td>
<td>0.17 ± 0.06</td>
<td>/</td>
</tr>
<tr>
<td>2CMC</td>
<td>0.41 ± 0.16</td>
<td>0.41 ± 0.53</td>
<td>0.41 ± 0.40</td>
<td>&gt;30.15</td>
<td>3.38 ± 1.07</td>
<td>0.29 ± 0.18</td>
<td>1.02 ± 0.70</td>
</tr>
<tr>
<td>R1479</td>
<td>2.95 ± 0.88</td>
<td>2.76 ± 0.89</td>
<td>1.98 ± 0.50</td>
<td>1.16 ± 0.43</td>
<td>28.63 ± 8.68</td>
<td>2.16 ± 0.27</td>
<td>/</td>
</tr>
<tr>
<td>BILN 2061</td>
<td>0.02 ± 0.01</td>
<td>&lt;0.004</td>
<td>0.004</td>
<td>0.04 ± 0.03</td>
<td>0.02 ± 0.01</td>
<td>1.25 ± 0.47</td>
<td>0.79 ± 0.08</td>
</tr>
<tr>
<td>VX-950</td>
<td>0.58 ± 0.10</td>
<td>0.36 ± 0.04</td>
<td>0.49 ± 0.32</td>
<td>1.01 ± 0.32</td>
<td>0.69 ± 0.15</td>
<td>0.31 ± 0.05</td>
<td>13.97 ± 1.4</td>
</tr>
</tbody>
</table>

EC<sub>50</sub>-values in µM

Alisporivir efficiently clears HCV replicons from the host cell


Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Alisporivir combination with Telaprevir.

VX-950 (7 µM)

Debio 025 (0.10 µM)

Debio 025 (0.10 µM) + VX-950 (7 µM)


Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus

The combination of Alisporivir with HCV protease or polymerase inhibitors prevents the development of drug escape mutants.

**Protease inhibitors**

- **Coelmont L. et al.** AAC 2009; 53: 967-976.

**Nucleoside and non-nucleoside polymerase inhibitor**


*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*
Clinical efficacy of Alisporivir

LETTER

Sustained virological response with 29 days of Debio 025 monotherapy in hepatitis C virus genotype 3

Patel and Heathcote, Gut, 2010

Flisiak et al., Hepatology (2009)
Selecting Alisporivir resistant replicons

Resistance selection is a long process:

- Alisporivir\textsuperscript{res}: $\pm$ 20 weeks
- CsA\textsuperscript{res}: $\pm$ 23 weeks

Coelmont et al., PLoS ONE, 2011

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
E320D contributes most to the resistance

Coelmont et al., PLoS ONE, 2011
## Prevalence of D320E in euHCV database

<table>
<thead>
<tr>
<th>Subtype</th>
<th># in EuHCVdb</th>
<th>NS3 A241P</th>
<th>WT&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Variant&lt;sup&gt;1&lt;/sup&gt;</th>
<th>NS5A R262Q</th>
<th>WT&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Variant&lt;sup&gt;1&lt;/sup&gt;</th>
<th>NS5A R318W</th>
<th>WT&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Variant&lt;sup&gt;1&lt;/sup&gt;</th>
<th>NS5A D320E</th>
<th>WT&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Variant&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>224</td>
<td>A (94%)</td>
<td>P (0%)</td>
<td>R (96%)</td>
<td>Q (0%)</td>
<td>R (100%)</td>
<td>W (0%)</td>
<td>D (100%)</td>
<td>E (0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>350</td>
<td>A (97%)</td>
<td>P (0%)</td>
<td>R (97%)</td>
<td>Q (0.8%)</td>
<td>R (98%)</td>
<td>W (0%)</td>
<td>D (99%)</td>
<td>E (0.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>19</td>
<td>A (100%)</td>
<td>P (0%)</td>
<td>del&lt;sup&gt;3&lt;/sup&gt; (85%)</td>
<td>Q (0%)</td>
<td>R (100%)</td>
<td>W (0%)</td>
<td>D (95%)</td>
<td>E (5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>25</td>
<td>A (100%)</td>
<td>P (0%)</td>
<td>del&lt;sup&gt;3&lt;/sup&gt; (100%)</td>
<td>Q (0%)</td>
<td>R (92%)</td>
<td>W (0%)</td>
<td>D (96%)</td>
<td>E (4%)</td>
<td></td>
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<tr>
<td>3</td>
<td>28</td>
<td>S (89%)</td>
<td>P (0%)</td>
<td>R (100%)</td>
<td>Q (0%)</td>
<td>R (100%)</td>
<td>W (0%)</td>
<td>D (100%)</td>
<td>E (0%)</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>39</td>
<td>A (77%)</td>
<td>P (0%)</td>
<td>del&lt;sup&gt;3&lt;/sup&gt; (88%), R(12%)</td>
<td>Q (0%)</td>
<td>R (87%)</td>
<td>W (0%)</td>
<td>D (82%)</td>
<td>E (5%)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<sup>1</sup>Variant identified in the Alisporivir<sub>res</sub> replicon

<sup>2</sup>WT AA for that genotype (AA with the highest prevalence)

<sup>3</sup>del=deletion

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Coelmont et al., PLoS ONE, 2011
Role of NS5A or NS5B in resistance

Resistant HCV subgenomic replicon

WT HCV subgenomic replicon

Coelmont et al., PLoS ONE, 2011
Swapping of NS5A results in transfer of resistance

Coelmont et al., PLoS ONE, 2011
Debio-025 differs from BMS-790052

NS5A inhibitors:

- redistribution of NS5A: aggregates of NS5A in cytoplasm
- reduce hyperphosphorylation of NS5A

DEB025:

- no redistribution of NS5A observed
- no reduced hyperphosphorylation of NS5A

Coelmont et al., PLoS ONE, 2011
Alisporivirres RNA is less dependent on CypA for replication

Coelmont et al., PLoS ONE, 2011

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Mutations in Alisporivirres NS5A do not preserve the integrity of the interaction NS5A - CypA

NS5A protein is a substrate for the peptidyl-prolyl cis/trans isomerase activity of cyclophilins A and B.

Coelmont et al., PLoS ONE, 2011

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Mutations in Alisporivir\textsuperscript{res} NS5A do not preserve the integrity of the interaction NS5A - CypA

Coelmont et al., PLoS ONE, 2011
Shift in cis - trans balance between WT and D320E peptide

308-KFPRAMPIWARP DY NPPLLE-327  ↔  308-KFPRAMPIWARP EYNPPLLE-327

trans  ↔  cis
75.9%  24.1%

Shift in cis - trans balance between WT and D320E peptide

308-KFPRAMPIWARPEYNPPLLE-327  ↔  308-KFPRAMPIWARPDYNPPLLE-327

trans  ↔  cis
70.4%  29.6%

Coelmont et al., PLoS ONE, 2011

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Working hypothesis MOA CypA inhibitors

Normal situation:  
\[\text{NS5A} \rightarrow \text{HCV replication}\]

\textit{trans} to \textit{cis} isomerization

Alisporivir inhibition:  
\[\text{NS5A} \xrightarrow{\text{trans} \leftrightarrow \text{cis}} \rightarrow \text{HCV replication}\]

Alisporivir resistance:  
\[\text{DEB025}_{\text{res}} \text{NS5A} \xrightarrow{\text{trans} \leftrightarrow \text{cis}} \rightarrow \text{HCV replication}\]
Overall Conclusion

Current therapy is associated with serious side-effects and a large percentage of patients is not cured.

There are a number of excellent targets in the replication cycle of HCV for inhibition of viral replication.

In general drug resistant variants develop rapidly against NS3 protease inhibitors, NS5A inhibitors and NS5B non nucleoside polymerase inhibitors

Drug resistance does not readily develop against NS5B polymerase inhibitors and cyclophylin binding inhibitors.

Combination of three (or possible four) different potent and well tolerated compounds with a non-overlapping resistance profile will likely be the future therapy. This therapy should allow to cure a large percentage of chronically infected patients.
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