HIV ATTACHMENT INHIBITORS

Thomas Klimkait
Molecular Virology, Department Biomedicine – Petersplatz
University of Basel, Switzerland
“The lecture aims to have an **interactive character** to **educate junior physicians and researchers**, however throughout the years we have learned that a large number of the regular conference participants also attend”
Steps of HIV entry

1. Env - CD4-interaction
2. Binding of 2nd receptor
3. Membrane contact
4. Exposure fusion-domain (gp41)
5. Membrane fusion
6. Entry of intact nucleocapsid

⇒ Where can an “Attachment Inhibitor” interfere?
Why viruses control entry so tightly

• ... to find the most appropriate target cell
• ... to avoid getting “lost in translation”
• Viral note of caution: *Once you’re in wrong, you won’t get out!*

→ use of one specific or more receptors

NB:

• *Attachment is an “early event” only in acute infection*
• *In chronic HIV-infection it comes AFTER protease inhibition as the last step before RT*
HIV on its way in

a) Uptake via coated pits

b) Direct membrane fusion

Virus

Attachment

Fusion


Vaillant et al. 2006
Virus inhibition during cell approach

- **Soluble CD4** as competitor to receptor binding
- Inhibitors of **gp120 binding** to cell (CD4)
- Inhibitor of gp120 binding to **chemokine** receptor
- Preventing gp41/gp120 **conformational** change
- Blocking **exposure** of fusion **domain**
- Blocking **fusion event** (gp 41 bundle formation)
HIV induces fusion of membranes

HIV-induced fusion of hu lymphocytes

epitheloid cells (CD4+, CCR5+, CXCR4+)
Concepts: soluble receptor

Binding of soluble CD4 proteins to human immunodeficiency virus type 1 and infected cells induces release of envelope glycoprotein gp120

(acquired immunodeficiency syndrome/transmembrane glycoprotein/gp41/retrovirus)

TIMOTHY K. HART*, RICHARD KIRSH†, HARMA ELLEN Jr., RAYMOND W. SWEET§, DENNIS M. LAMBERT¶, STEPHEN R. PETTeway, JR.¶, JEFFREY LEARY¶, and PETER J. RUGELSKI*
Concepts: anti-envelope antibody

- Ibalizumab (TMB355/TNX355)
- "Potent neutralizing antibodies may provide a significant new weapon in the therapeutic arsenal against HIV and are expected to have fewer toxic side effects than current therapy. It is imperative that clinical studies like these be conducted if we are to make progress in the development of suitable vaccines against HIV. These studies will help define useful, affordable and viable vaccine studies in the future."

Jacobson, TANOX Biosystems, Houston, USA, 1995

Today by WuXi, Taimed Biologics

Low therapeutic potency; in trials for prevention

(new approaches attempt to use "broadly neutralizing Abs")
Concepts: antagonize the (co)receptor

Lead for Oncology (?)

Low bioavailability

Inferior to EFV (poor Phase III design)

Liver toxicity (no class-specific tox)

Escape:

- Selection of CXCR4-tropic HIV
- Resistant CCR5-tropic Virus

Westby M et al. 2004, Antiviral Therapy, 9, S10.
Enfuvirtide (T20): The peptide blocks 6-helix-bundle formation!

Dosing / longterm tolerability/compliance difficult!
Small inhibitory compound needed!
“Attachment Inhibitor”

I. Savant Landry, CROI 2015

Gastrointestinal lumen

BMS-663068 (prodrug)

Alkaline phosphatase

BMS-626529 (active moiety)

BMS-626529

Blood plasma
Optimizing antiviral properties

Piperazine derivatives are highly potent in vitro!

- **BMS-378806**
  - EC$_{50}$: 1.47 nM
  - CC$_{50}$: >300 μM
  - Lin et al. 2003. PNAS. 100(19):11013

- **BMS-488043**
  - EC$_{50}$: 0.88 nM
  - CC$_{50}$: >300 μM
  - Wang et al. 2009. JMedChem. 52:7778-7787

- **BMS-626529**
  - EC$_{50}$: 0.4 nM
  - CC$_{50}$: >300 μM
  - Nowicka-Sans. 2012. AAC. 56(7):3498-3507
Chemical optimization (in vitro)

Metabolic parameters for chemical optimization of leads
Proof of concept (Virus reduction)

BMS-448043
(today as prodrug BMS-626529, Fostemsavir)

--- Treatment period  ➔  --- washout period  ➔
Bristol-Myers Squibb Receives Breakthrough Designation for HIV Treatment

An FDA breakthrough designation speeds the development and review of therapies that treat extremely serious conditions

By ANGELA CHEN
July 21, 2015 9:40 a.m. ET

Bristol-Myers Squibb Co. said Tuesday that the U.S. Food and Drug Administration has granted breakthrough designation for its HIV treatment for users who have become accustomed to most other treatment options.

Compound today developed by ViiV Healthcare/GSK
Safety and efficacy of the HIV-1 attachment inhibitor prodrug BMS-663068 in treatment-experienced individuals: 24 week results of AI438011, a phase 2b, randomised controlled trial

Jacob P Lalezari, Gulam H Latiff, Cynthia Brinson, Juan Echevarría, Sandra Treviño-Pérez, Johannes R Bogner, Melanie Thompson, Jan Fourie, Otto A Sussmann Pena, Fernando C Mendo Urbina, Marcelo Martins, Iulian G Diaconescu, David A Stock, Samit R Joshi, George J Hanna, Max Lataillade, for the AI438011 study team
Clinical performance

AI438011: Mean Change in CD4+ T-cell Counts from Baseline through Week 24: Observed*

AI438011: BMS-663068 Monotherapy Substudy: Mean Change in HIV-1 RNA from Baseline*

*Error bars represent standard error of the mean.
AI438011: Proportion of Subjects Achieving HIV-1 RNA <50 c/mL by Baseline Viral Load:

- Yellow bars: Baseline viral load < 100,000 c/mL
- Blue bars: Baseline viral load ≥ 100,000 c/mL

<table>
<thead>
<tr>
<th>Dose</th>
<th>BID</th>
<th>QD</th>
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<tbody>
<tr>
<td>400 mg</td>
<td>800 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>BID</td>
<td>BID</td>
<td>QD</td>
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<tr>
<td>BMS-663068</td>
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No escape by CD4-independence(!)

Activity of the HIV-1 Attachment Inhibitor BMS-626529, the Active Component of the Prodrug BMS-663068, against CD4-Independent Viruses and HIV-1 Envelopes Resistant to Other Entry Inhibitors

Zhufang Li, Nannan Zhou, Yongnian Sun, Neelanjana Ray, Max Lataillade, George J. Hanna, Mark Krystal

Some association between maraviroc resistance and reduced susceptibility to BMS-626529(?), but absolute correlation cannot be presumed, since some CCR5-tropic maraviroc-resistant envelopes remained sensitive to BMS-626529.
Clinical use is unlikely to promote resistance via generation of CD4-independent virus.
Will there be resistance?

• Mutation **M426L** was found to be the primary substitution associated with nonresponse to BMS-626529.

• The M426L substitution was absent at baseline in 1 nonresponder, who instead harbored substitutions at other positions associated with resistance to BMS-626529 and BMS-448043 (M434I and S375M).

• M426L was also found to be present in 2 responders.

→ While the presence of the M426L substitution at baseline does not entirely preclude response, it does seem to be predictive of nonresponse to BMS-663068.

*Ray et al. J Acquir Immune Defic Syndr* Volume 64(1) September 1, 2013
Other entry inhibitors not affected

Susceptibilities of BMS–626529–resistant clinical samples to other entry inhibitors

<table>
<thead>
<tr>
<th>Subject (clone)</th>
<th>Tropism</th>
<th>BMS–626529 resistance substitution(s)</th>
<th>Mean fold change in EC50 ± SD</th>
<th>Mean EC50 (nM) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 (1)</td>
<td>CCR5</td>
<td>M426L/M475I</td>
<td>2,932 ± 404</td>
<td>7.4 ± 1.3</td>
</tr>
<tr>
<td>21 (170)</td>
<td>CCR5</td>
<td>M426L</td>
<td>386 ± 95</td>
<td>9.2 ± 1.8</td>
</tr>
<tr>
<td>21 (169)</td>
<td>CXCR4</td>
<td>M426L</td>
<td>215 ± 76</td>
<td>&gt;5,000</td>
</tr>
<tr>
<td>41 (33)</td>
<td>CCR5</td>
<td>S375M/M434I</td>
<td>&gt;19,418</td>
<td>4.0 ± 0.1</td>
</tr>
</tbody>
</table>

Issues to be addressed

• Reduced baseline susceptibility found in 12% of patients due to envelope polymorphisms
  \( \text{(screened by baseline IC}_{50}\text{)} \)

• Are there subtype differences in response?

• Resistance profile in long-term therapy?
By the way...

My laboratory is looking for a motivated
- Postdoc
- PhD-student

-- feel free to contact me --