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Our Issues, Our Drugs, Our Patients

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HIV life cycle revisited: What’s new in basic science?

Theresa Rossouw
Outline of the Presentation

• Lifecycle overview
• New drugs & therapies
• Cell entry
  – Co-receptor binding
  – Attachment
Keeping it Simple
Need for New & Novel Treatment

• Class resistance
• Transmission of resistant viruses
• Treatment fatigue
• Serious drug-associated pathology
# New Options on the Horizon

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>NNRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir alafenamide (TAF)</td>
<td>Doravirine</td>
</tr>
<tr>
<td>MK-8591</td>
<td>GSK 2248761 (IDX899)</td>
</tr>
<tr>
<td>Apricitabine</td>
<td>RDEA806</td>
</tr>
<tr>
<td>Elvucitabine</td>
<td>Lersivirine</td>
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<tr>
<td>Racivir</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PIs</th>
<th>INSTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP-518</td>
<td>Elvitegravir</td>
</tr>
<tr>
<td>GS-8374</td>
<td>Dolutegravir</td>
</tr>
<tr>
<td>PPL-100</td>
<td>Cabotegravir</td>
</tr>
<tr>
<td></td>
<td>GSK-572</td>
</tr>
</tbody>
</table>
Novel Treatment Options

- Maturation inhibitor
  - BMS-955176
  - Vivecon (MP-9055)
- New target: Rev-mediated viral RNA biogenesis
  - ABX464
- Monoclonal antibodies
  - Broadly neutralising antibody VRC01
  - Anti-PD-1 (pembrolizumab)
  - CD4 - TNX-355, TBM-360
- eCD4-Ig
- TLR7 agonist
  - GS9620 – reversal of latency
- Genetic therapy & stem cell research
Entry Inhibition

• Act outside the cell
• No concerns about:
  – Intracellular drug penetration
  – Interactions with drugs metabolized by cytochrome P450
    • PIs and NNRTIs
  – Disruptions of lipid homeostasis
Entry Inhibition

Attachment
DC-SIGN

CD4 Binding
PRO 542 Other Ab

Coreceptor Binding
CCR5 CXCR4
SCH-C AMD3100
SCH-D ALX40-4C
TAK779 T22
PRO 140

Hairpin Formation and Membrane Fusion
T-20 T-1249
5-Helix
Co-receptors

• Most infections result from virus strains that use CCR5 in addition to CD4 to infect cells
  – R5 virus strains
  – Predominate in first few years

• Mutations may accumulate in Env that enable it to use CXCR4
  – X4 or R5X4 strains
  – Accelerated disease progression
  – In part because CXCR4 is expressed on a much greater fraction of CD4+ T cells than CCR5
18% of Northern Europeans lack CCR5 due to a naturally occurring polymorphism in the CCR5 open reading frame—CCR5 δ32.

These individuals are highly resistant to HIV infection. People with naturally reduced CCR5 expression experience slower HIV disease progression.
## Flurry of New CCR5 Antagonists

First anti-HIV agents that target host proteins rather than viral enzymes or proteins

<table>
<thead>
<tr>
<th>CCR5 inhibitors</th>
<th>Company</th>
<th>Status</th>
<th>Disease</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAK-652 (TBR-652)</td>
<td>Takeda/Tobira</td>
<td>Phase II</td>
<td>HIV</td>
<td>A potent, orally bioavailable CCR5 antagonist</td>
</tr>
<tr>
<td>Aplaviroc</td>
<td>Ono</td>
<td>Terminated (Phase II/III)</td>
<td>HIV</td>
<td>Aplaviroc's development was stopped because of hepatotoxicity</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Pfizer</td>
<td>Approved by US FDA</td>
<td>HIV</td>
<td>The first FDA-approved CCR5 antagonist</td>
</tr>
<tr>
<td>PF-232798</td>
<td>Pfizer</td>
<td>Phase II</td>
<td>HIV</td>
<td>A second-generation Pfizer oral CCR5 antagonist</td>
</tr>
<tr>
<td>Vicriviroc</td>
<td>Schering-Plough/Merck</td>
<td>Terminated (Phase III)</td>
<td>HIV</td>
<td>Vicriviroc did not meet the primary efficacy endpoint</td>
</tr>
<tr>
<td>INCB9471</td>
<td>Incyte</td>
<td>Phase II</td>
<td>HIV</td>
<td>A new class of oral CCR5 antagonist</td>
</tr>
</tbody>
</table>
CCR5/CCR2 Inhibitor

- Cenicriviroc (formerly TBR-652)
- CCR2 receptor binds to monocyte chemo-attractant protein 1 (MCP-1)
  - Promotes migration of monocytes
  - Role in inflammation
  - Implicated in a range of conditions including liver fibrosis, metabolic syndrome and cardiovascular disease.
- Phase II
  - Lower sCD14
    - High sCD14 independent predictor of all-cause death in SMART
- High drop-out rate because of a complicated dosing
Resistance

• Two mechanisms
  – Changing the way it uses co-receptors
    • Use the same co-receptor but in a drug-bound form
    • Many mutations in gp120 region of HIV-1 Env, especially in the V2 and V3 regions
  – Switching co-receptor usage
    • CCR5 $\rightarrow$ CXCR4
Concern with Blocking CCR5

Original Article

CRF19_cpx is an Evolutionary fit HIV-1 Variant Strongly Associated With Rapid Progression to AIDS in Cuba
Concerns with Blocking CCR5

• Current consensus: CCR5 & CXCR4 are major co-receptors
• Additional chemokine receptors have been reported to act as alternative co-receptors for CD4 when they are over-expressed
  – CCR2b, CCR3, CCR8, CCR9, CXCR6, CXCR1
Safety Concerns

• Normal function of CCR5 & CXCR4 not fully understood
• Might disrupt normal immune function
• CCR5 δ32 mutation
  – No serious or life-threatening immunological impairment
  – But some degree of immune dysfunction
    • Lower risk of organ rejection after transplantation
    • Lower likelihood of clearing hepatitis C virus
    • Higher risk of symptomatic West Nile virus infection
• Genetically engineered CCR5-deficient mice have impaired immune responses to certain OIs
Interest in Blocking CXCR4

• Interaction between CXCR4 and its ligand SDF-1 is involved in various disease conditions
  – cancer cell metastasis
  – leukemia cell proliferation
  – rheumatoid arthritis
  – pulmonary fibrosis
  – CXCR4 is expressed in >23 human cancers – breast, ovarian, hepatocellular, hematological, lung, brain, prostate

• CXCR4 inhibitors have potential as novel therapeutics for the treatment of these diseases as well as HIV infection
# CXCR4 Antagonists

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Stage of development</th>
<th>Disease</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALX40-4C</td>
<td>NPS Allelix</td>
<td>Terminated (Phase I/II)</td>
<td>HIV</td>
<td>No apparent effect was observed on viral load</td>
</tr>
<tr>
<td>AMD3100</td>
<td>AnorMED</td>
<td>Terminated (Phase I/II)</td>
<td>HIV</td>
<td>Little effect was observed on viral load</td>
</tr>
<tr>
<td>AMD3100</td>
<td>Genzyme</td>
<td>Approved by US FDA</td>
<td>Stem cell mobilizer</td>
<td>Use in combination with G-CSF</td>
</tr>
<tr>
<td>AMD3100</td>
<td>Genzyme</td>
<td>Suspended (Phase I/II)</td>
<td>HIV</td>
<td>A derivative of AMD3100 that can be orally administered. Liver histology changes were observed in long-term preclinical toxicity experiments.</td>
</tr>
<tr>
<td>T140</td>
<td>Kyoto University</td>
<td>Preclinical</td>
<td>HIV, cancer metastasis, leukemia, rheumatoid arthritis</td>
<td>A downsized analog of T22 peptide that specifically inhibits CXCR4</td>
</tr>
<tr>
<td>KRH-3955</td>
<td>Kureha</td>
<td>Preclinical</td>
<td>HIV, cancer metastasis</td>
<td>A highly potent, orally bioavailable CXCR4 antagonist</td>
</tr>
</tbody>
</table>
Safety Concerns

• Even less is known blocking CXCR4
• CXCR4 is expressed in a wide variety of normal tissues
  – lymphoid tissues, thymus, brain, spleen, stomach & small intestine
• Mice lacking CXCR4 have abnormal hematopoiesis, cardiogenesis & vascularization
• SDF-1/CXCR4 interaction is critical for:
  – retention of hematopoietic stem cells in BM
  – foetal hematopoiesis
New Strategies

CD4 Attachment Inhibitor – BMS-663068 (fostemsavir)

Figure 2

[Diagram showing the mechanism of action of the CD4 attachment inhibitor (fostemsavir), BMS-663068, compared to a control with no drug. The diagram illustrates the effect of the drug on conformational changes and CD4 binding, highlighting BMS-626529 binding.]
Combinectin (BMS-986197)

• Novel recombinant biologic molecule
• 3 independent & synergistic modes of blocking HIV entry
• Potential as single long-acting regimen for HIV-1 as a self-administered s/c weekly injection
• Adnectins are small proteins
  – Derived from human fibronectin protein
  – Modifiable binding loops resembling certain antibody regions
Combinectin

1. Anti-CD4 adnectin: allows binding to the receptor, but prevents conformational changes needed for binding to co-receptors
2. Anti-gp41 adnectin: attacks the N17 sequence of the HIV gp41 envelope protein subunit
3. Alpha-helical peptide fusion inhibitor: works similarly to enfuvirtide

Human serum albumin (HSA) molecule: optimize in vivo PK

Early laboratory and animal studies
Conclusion

• New options on the horizon
  – Less toxic
  – Less frequent dosing
  – Possibly even self-administered injections

• More options for patients with drug-resistant virus
Thank You