Antiviral Agents

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Challenges to the Development of Effective Antiviral Agents

• Myriad number of agents
• Need knowledge of replication at molecular level to define targets
  – Viruses as intracellular parasites make targeting more difficult to avoid host toxicity
• Lack of culture systems for some agents hinders development
• High through-put screening plus ‘rational’ drug design are both labor intensive and expensive
Challenges to the Development of Effective Antiviral Agents

• Pathogenesis of certain agents makes therapy a challenge even in the face of defined targets

• Clinical presentation of acute viral infections may be at peak of viral replication in vivo
  – May have a small window to intervene effectively
  – Need rapid diagnostic procedures

Diagnosis of Viral Infections

• Clinical suspicion
  – Is syndrome diagnostic of a specific entity?
  – Is viral disease in the differential diagnosis of a presenting syndrome?

• Knowledge of appropriate specimen(s) to send
  – Blood
  – Body fluids
  – Lesion scraping
  – Tissue
  – Proper transport is essential
Herpes Zoster

Progress in Antiviral Therapy

<table>
<thead>
<tr>
<th>Virus Family</th>
<th>Antiviral Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpesviruses (HSV, VZV, CMV)</td>
<td>Acyclovir, famciclovir, valacyclovir, ganciclovir, cidofovir, formivirsen, valganciclovir</td>
</tr>
<tr>
<td>HIV-1</td>
<td>21 approved agents</td>
</tr>
<tr>
<td>Influenza</td>
<td>Amantadine, rimantadine, ribavirin, oseltamivir</td>
</tr>
<tr>
<td>Resp. syncytial virus</td>
<td>Ribavirin, RSV immune globulin, palivizumab</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>3TC, FTC, adefovir, tenofovir, entecavir</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>pegIFN-ribavirin</td>
</tr>
<tr>
<td>Papillomaviruses</td>
<td>IFN, cidofovir</td>
</tr>
<tr>
<td>JC virus</td>
<td>Cidofovir</td>
</tr>
<tr>
<td>Picornaviruses</td>
<td>Pleconaril</td>
</tr>
<tr>
<td>Rhinoviruses</td>
<td>Tremacamra (rsICAM-1)</td>
</tr>
</tbody>
</table>
Non-HIV Antiviral Therapy: Targets

• Herpesviruses
• Respiratory viruses
• Hepatitis viruses
• Others

Anti-Herpesvirus Agents

• Acyclovir
• Valacyclovir
• Famiciclovir
• Ganciclovir
• Valganciclovir
• Foscarnet
• Cidofovir
• Formivirsen
• Trifluridine
• Idoxuridine
### Anti-Herpesvirus Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Active Moiety</th>
<th>Target Agents</th>
<th>Route of Admin</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Acyclic nucleoside</td>
<td>Tri-phosphate</td>
<td>HSV, VZV</td>
<td>Oral, intravenous, topical</td>
<td>Renal, Neuro</td>
</tr>
<tr>
<td>Val-ACV</td>
<td>Ester prodrug of acyclovir</td>
<td>Tri-phosphate</td>
<td>HSV, VZV</td>
<td>Oral</td>
<td>Renal, Neuro</td>
</tr>
<tr>
<td>Penciclovir</td>
<td>Acyclic nucleoside</td>
<td>Tri-phosphate</td>
<td>HSV</td>
<td>Topical</td>
<td>Local irritation</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>Ester prodrug of penciclovir</td>
<td>Tri-phosphate</td>
<td>HSV, VZV</td>
<td>Oral</td>
<td>Headache, nausea,</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Acyclic nucleoside</td>
<td>Tri-phosphate</td>
<td>CMV, HSV, VZV</td>
<td>Intravenous, oral, intraocular</td>
<td>Hematologic</td>
</tr>
<tr>
<td>Val-GCV</td>
<td>Ester prodrug of ganciclovir</td>
<td>Tri-phosphate</td>
<td>CMV</td>
<td>Oral</td>
<td>Hematologic</td>
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<tr>
<td>Foscarnet</td>
<td>Pyrophosphate analog</td>
<td>Parent drug active</td>
<td>CMV, HSV</td>
<td>Intravenous</td>
<td>Renal, metabolic</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Nucleotide analog</td>
<td>Di-phosphate</td>
<td>CMV, HSV, HPV, pox</td>
<td>Intravenous</td>
<td>Renal, ocular</td>
</tr>
<tr>
<td>Formiviren</td>
<td>Antisense oligo-NT: binds to CMV mRNA</td>
<td>Parent drug active</td>
<td>CMV</td>
<td>Intraocular</td>
<td>Ocular</td>
</tr>
<tr>
<td>Trifluridine</td>
<td>Nucleoside analog</td>
<td>Tri-phosphate</td>
<td>HSV keratitis</td>
<td>Topical</td>
<td>Ocular</td>
</tr>
<tr>
<td>Idoxuridine</td>
<td>Nucleoside analog</td>
<td>Tri-phosphate</td>
<td>HSV keratitis</td>
<td>Topical</td>
<td>Ocular</td>
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Anti-Herpesvirus Agents

![Chemical structures of antiherpesviral agents.](image)

**FIGURE 11-1.** Chemical structures of antiherpesviral agents.
Acyclovir I

- Development represents a watershed in the field of antiviral chemotherapy
- Acyclic guanosine analog
- Active vs. HSV, VZV and modestly CMV
- Mechanism of action
  - Preferentially taken up by virally infected cells
  - Monophosphorylated by virally encoded thymidine kinases
  - Di- and triphosphorylation completed by cellular kinases
  - ACV-TP is the active moiety
    - Competitive inhibitor of viral DNA polymerase
      - Cellular DNA polymerases much less susceptible to inhibition
    - Leads to viral DNA chain termination

Acyclovir: Mechanism of Action
Acyclovir II

• Pharmacology
  – Administered by oral, intravenous and topical routes
  – Oral bioavailability 15-30%
  – T₁/₂ 3 hrs
  – Primarily renally excreted

• Toxicities
  – Headache, nausea
  – Renal
  – Neurologic

• Resistance
  – Mediated by mutations in viral thymidine kinase and/or viral DNA polymerase genes
    • TK-deficient and TK altered virus can be produced
  – Clinically significant infections can be caused by drug resistant HSV and VZV

Anti-Respiratory Virus Agents

• Amantadine
• Rimantadine
• Zanamivir
• Oseltamivir
• Ribavirin
Amantadine and Rimantadine

- Tricyclic amines
- Active vs. influenza A only at clinically achievable concentrations
- Mechanism of action
  - Interference with function of viral M2 protein
    - M2 protein acts as an ion channel facilitating the hydrogen ion mediated dissociation of the matrix protein from the nucleocapsid
- Pharmacology:
  - Orally bioavailable
  - Amantadine: renal excretion
  - Rimantadine: hepatic metabolism and renal excretion
- Major toxicity
  - Neurotoxicity: amantadine > rimantadine
- Useful for treatment and prophylaxis of influenza A infections
- Resistance mediated by mutations in M2 coding region

**FIGURE 11-7.** Chemical structures of amantadine and rimantadine.
Influenza Virus Replication Cycle

Uncoating of Influenza Virus

From Fields Virology
Zanamivir and Oseltamivir I

• Active vs. influenza A and B
• Mechanism of action
  – Neuraminidase inhibitors
    • Viral neuraminidase catalyzes cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids, a process necessary for release of virus from host cell surfaces
    • Oseltamivir is an ester prodrug of GS4071, oseltamivir carboxylate
      • Transition state analog of sialic acid
        – Binds to viral neuraminidase

Influenza Virus Replication Cycle

From Fields Virology
Zanamivir and Oseltamivir II

• **Pharmacology**
  - Zanamavir
    • Oral inhalation
  - Oseltamivir
    • Orally bioavailable
    • Converted from ester prodrug to active form
    • Renally excreted

• **Toxicities**
  - Exacerbation of reactive airway disease by zanamavir
  - Nausea and vomiting for oseltamivir

Zanamivir and Oseltamivir III

![](image1.png)

SIALIC ACID

GG 167
Zanamivir

DANA

Oseltamivir
GS 4071
Zanamivir and Oseltamivir IV

• **Indications**
  – Treatment of influenza A and B within 24-48 hrs of symptom onset
  – Prophylaxis
  – N.B.: Neither drug interferes with antibody response to influenza vaccination

• **Resistance**
  – Reports beginning to appear in literature

Ribavirin I

• **Synthetic nucleoside analog**
• **Active vs. broad range of RNA and DNA viruses**
  – Flavi-, paramyxo-, bunya-, arena-, retro-, herpes-, adeno-, and poxviruses
• **Mechanism of action complex**
  – Triphosphorylated by host cell enzymes
    - For influenza
      – Ribavirin-TP interferes with capping and elongation of mRNA and may inhibit viral RNA polymerase
    - For other agents
      – Ribavirin-MP inhibits inosine-5’-monophosphate dehydrogenase depleting intracellular nucleotide pools, particularly GTP
Ribavirin II

• Pharmacology
  – Aerosol and oral administration
  – Hepatically metabolized and renally excreted

• Major toxicity
  – Anemia

• Indications
  – Aerosol treatment of RSV in children
    • Effectiveness debated
  – Oral treatment of HCV (in combination with pegylated IFN-alpha)

Anti-Hepatitis Agents

• Hepatitis B
  – Lamivudine
    • Nucleoside analog first developed for HIV
    • Lower dose used for HBV (100 mg/day)
  – Adefovir dipivoxil
    • Nucleotide analog first developed for HIV but nephrotoxic at higher doses
    • Approved for HBV at lower dose (10 mg/day)
  – Entecavir
    • Most recently approved anti-HBV agent

• Hepatitis C
  – Interferon-alpha (pegylated)
  – Ribavirin
Interferons I

- Part of cytokine repertoire
- Possess antiviral, immunomodulatory and antiproliferative effects
- Types
  - Alpha/Beta (leukocyte/fibroblast)
    - Coding genes located on chromosome 9
    - At least 24 subtypes of alpha, 1 of beta
  - Gamma
    - Coding gene located on chromosome 12
    - 1 subtype

Interferons II: Mechanism of Action

- Act by inducing an antiviral state within cells
- Bind to specific receptors on cell surface
- Receptor associated tyrosine kinases activated
  - Tyk2 and JAK 1 for alpha and beta
  - JAK1 and JAK2 for gamma
- Cytoplasmic proteins (STAT) phosphorylated
  - Move to nucleus and bind to cis-acting elements in promoter regions of IFN inducible genes
Interferons III: Mechanisms of Action

- Synthesis of 2'-5' oligoadenylate synthetase
  - Activated by dsRNA
  - Convert ATP into a series of 2'-5' oligo(A)s
    - These activate RNAse L which cleaves single stranded mRNAs
- Synthesis of dsRNA-dependent protein kinase (PKR, eIF-2 kinase)
  - PKR activated by dsRNA and autophosphorylated
    - In turn, phosphorylates alpha subunit of eukaryotic initiation factor 2
    - Protein synthesis inhibited
- Induction of a phosphodiesterase with inhibition of peptide chain elongation
- Synthesis of MxA protein which can bind to cytoskeletal proteins and inhibit viral transcriptases
- Induction of nitric oxide by gamma IFN in macrophages

Interferons IV

- Pharmacology
  - Injected IM or SC
  - Renal excretion and inactivation in body fluids/tissues
- Toxicities
  - Flu-like symptoms
  - HematoLogic effects
    - Leukopenia and thrombocytopenia
  - Neuropsychiatric effects
- Antiviral indications
  - IFN-alpha (pegylated) SC for HCV (in combination with ribavirin)
  - Intralesional for condyloma acuminata
- Resistance can develop
  - Mutations in NS5A gene of HCV described
Passive Immunization for Viral Infections I

- Human immune globulin
  - Prevention of hepatitis A
  - Prophylaxis and treatment of enterovirus infections in neonates and in children with antibody deficiency
  - Treatment of B19 parvovirus infection in immunodeficient individuals

- CMV immune globulin
  - Prophylaxis of CMV in solid organ transplant recipients
  - Treatment of CMV pneumonia in combination with ganciclovir

- Hepatitis B immune globulin
  - Prophylaxis of hepatitis B infection

- Rabies immune globulin
  - Post-exposure prophylaxis for rabies (in combination with rabies vaccine)

Passive Immunization for Viral Infections II

- Respiratory syncytial virus immune globulin
  - Prevention of complications of RSV infection in young children

- Palivizumab
  - Humanized RSV monoclonal antibody
  - Prevention of complications of RSV infection in young children

- Varicella-zoster immune globulin
  - Prevention of varicella infection in immunocompromised children and adults within 96 hours of exposure

- Vaccinia immune globulin
  - Available from CDC for complications of smallpox (vaccinia) vaccination
Conclusions

• Field of antiviral therapy has matured dramatically in past 30 years
• Greatest progress made for
  – Herpesviruses
  – HIV
  – Respiratory viruses
  – Hepatitis viruses
• Preventive vaccination remains the key to global control of viral infections