Viruses

Obligate Intracellular Parasites

Virus Particle (Virion) protect genome facilitate entry

Replication--1 virus can yield 10-100,000 progeny
Lecture 1
Introduction/history of virology

Lecture 2
vertebrate virus families and virus classification
structure
virus-receptor interactions

Lecture 3
Entry

Lecture 4
Replication

Lecture 5
Assembly and Release
Steps in Infection of Cells  Overview

1. **Encounter**--Virus in proximity of susceptible cells: lecture 2

2. **Attachment**--Virus Binding to Cell Surfaces: lecture 2

3. **Entry**--Insertion of Viral Genome: lecture 3

4. **Replication**--Synthesis of components of Virions: lecture 4

5. **Assembly**--formation of progeny virions: lecture 5

6. **Release**--release of progeny virus from infected cells: lecture 5
Principles of Structure, Virus Binding, Cell Entry, Replication, and Assembly

General Principles

Model Systems---used to Illustrate Principles

**Picornaviruses** (small, RNA viruses)
- nonenveloped
- positive-stranded RNA

**Influenza viruses**
- enveloped
- negative-stranded RNA
Virus Classification

APPROXIMATELY 36 FAMILIES OF VIRUSES (vertebrate)

CLASSIFICATION BASED ON:

VIRION STRUCTURE

VIRUS REPLICATION CYCLES
VIRION STRUCTURE

All Viruses have two components
Genome
Protein (capsid or nucleocapsid)

Some Viruses have, in addition, a membrane.

Non-enveloped (no membrane)

Enveloped (membrane)

Genome inside capsid
Examples of Non-enveloped Viruses

Rotavirus

Adenovirus

Hepatitis A
Examples of Enveloped Viruses

- influenza
- Ebola
- HIV
- Hepatitis B
- Vaccinia (small pox vaccine)
- rabies
- SARS
Togavirus

Semliki Forest Virus (like EEE)

Enveloped but structure very ordered

Flavivirus

Dengue virus (like West Nile)
Relative Sizes of Viruses
Virion Structure: Genomes

RNA
a. single stranded
   positive stranded
   negative stranded
b. double stranded (reoviruses)

segmented or non-segmented

DNA
do double stranded (most)
single stranded (parvoviruses)
Genomes

Size variable

RNA  7.5-30 kb
DNA

3.2 (HBV), 7.9 (HPV),
375 kbpairs (Herpes)

Predicts coding capacity

Expand coding capacity
splicing
Different ORFS
use both DNA strands for gene expression
RNA Virus Families

**7. Myxoviruses (influenza)**
(associated with mucous of respiratory tract -- common name is Influenza)

**8. Paramyxoviruses**
(originally identified as myxovirus and subsequently reclassified as "para" myxo), measles, mumps, respiratory syncytial virus, parainfluenza viruses, metapneumovirus, hendra virus, Nipah virus

**9. Coronaviruses**
(virus looks like it has a corona in electron micrographs), SARS

**10. Arenaviruses**
(virus looks like an arena in electron micrographs), LCMV, lassa fever virus

**11. Retroviruses**
(converts RNA to DNA therefore retro), HIV, HTLV

**12. Reoviruses**
(acronym = Respiratory Enteric Orphan), rotavirus

**13. Picornaviruses**
(small or pico RNA virus), polio, hepatitis A, Coxsackie viruses, Echoviruses

**14. Caliciviruses**
(calix refers to cuplike surface depressions on virion)

**15. Rhabdoviruses**
(bullet shaped), rabies

**16. Togaviruses**
(cloaked or enveloped), Eastern equine encephalitis virus or EEE

**17. Flaviviruses**
(named after yellow fever, a member of the group; yellow = flavus), also hepatitis C, Dengue virus, West Nile Virus

**18. Bunyaviruses**
(named after member of group, bunyamwera virus), hantavirus

**19. Bornaviruses**
(named after BDV, Borna disease virus, isolated in Borna, Germany)

**20. Astroviruses**
(from Latin -- "threadlike"), Marburg, Ebola
### Table 2.1: Summary Characteristics of Vertebrate Virus Families

<table>
<thead>
<tr>
<th>Family</th>
<th>Nucleocapsid morphology</th>
<th>Envelope</th>
<th>Virion morphology</th>
<th>Genome</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative sense ssRNA viruses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bornaviridae</td>
<td>ND</td>
<td>Yes</td>
<td>Spherical</td>
<td>1 – linear, 9 kb</td>
<td>V</td>
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<tr>
<td>Deltavirus</td>
<td>Isometric</td>
<td>Yes</td>
<td>Spherical</td>
<td>1 – circular, 2 kb</td>
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<tr>
<td>Filoviridae</td>
<td>Helical filaments</td>
<td>Yes</td>
<td>Bacilliform, filamentous</td>
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<tr>
<td>Orthomyxoviridae</td>
<td>Helical filaments</td>
<td>Yes</td>
<td>Pleomorphic, spherical</td>
<td>6–8 – linear, 10–15 kb</td>
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<tr>
<td>Paramyxoviridae</td>
<td>Helical filaments</td>
<td>Yes</td>
<td>Pleomorphic, spherical, filamentous</td>
<td>1 – linear, 13–18 kb</td>
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<tr>
<td>Rhabdoviridae</td>
<td>Coiled helical filaments</td>
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<td>Bullet shaped</td>
<td>1 – linear, 11–15 kb</td>
<td>V, I, P</td>
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<td><strong>Positive sense ssRNA viruses</strong></td>
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<tr>
<td>Arteriviridae</td>
<td>Linear, asymmetric</td>
<td>Yes</td>
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<td>1 + linear, 13–16 kb</td>
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<td>Astroviridae</td>
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<td>1 + linear, 6–8 kb</td>
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<tr>
<td>Caliciviridae</td>
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<td>No</td>
<td>Icosahedral</td>
<td>1 + linear, 7–8 kb</td>
<td>V</td>
</tr>
<tr>
<td>Coronaviridae</td>
<td>Helical</td>
<td>Yes</td>
<td>Spherical</td>
<td>1 + linear, 26–32 kb</td>
<td>V</td>
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<tr>
<td>Flaviviridae</td>
<td>Spherical</td>
<td>Yes</td>
<td>Spherical</td>
<td>1 + linear, 9–13 kb</td>
<td>V, I</td>
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<td>Hepeivirus</td>
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<td>Nodaviridae</td>
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<td>No</td>
<td>Icosahedral</td>
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<td>V, I</td>
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<tr>
<td>Picornaviridae</td>
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<td>1 + linear, 7–9 kb</td>
<td>V</td>
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<tr>
<td>Togaviridae</td>
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<td>Spherical</td>
<td>1 + linear, 10–12 kb</td>
<td>V, I</td>
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<tr>
<td>Arenaviridae</td>
<td>Filamentous</td>
<td>Yes</td>
<td>Spherical</td>
<td>2 ± linear, 11 kb</td>
<td>V</td>
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<tr>
<td>Bunyaviridae</td>
<td>Filamentous</td>
<td>Yes</td>
<td>Spherical</td>
<td>3 – or ± linear, 11–19 kb</td>
<td>V, I, P</td>
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<td><strong>Subviral agents: prions</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prions</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>ssRNA reverse transcribing viruses</strong></td>
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<td>Metaviridae</td>
<td>Spherical</td>
<td>Yes</td>
<td>Spherical</td>
<td>1 + linear, 4–10 kb</td>
<td>F, I, P, V</td>
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<td>Retroviridae</td>
<td>Spherical, rod or cone shaped</td>
<td>Yes</td>
<td>Spherical</td>
<td>1 + linear dimer, 7–13 kb</td>
<td>V</td>
</tr>
<tr>
<td><strong>dsRNA viruses</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Birnaviridae</td>
<td>Icosahedral</td>
<td>No</td>
<td>Icosahedral</td>
<td>2 ds linear, 5–6 kb</td>
<td>V, I</td>
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<tr>
<td>Picobirnaviridae</td>
<td>Icosahedral</td>
<td>No</td>
<td>Icosahedral, layered</td>
<td>10–12 ds linear, 19–32 kb</td>
<td>V, I, P, F</td>
</tr>
<tr>
<td>Reoviridae</td>
<td>Icosahedral</td>
<td>No</td>
<td>Icosahedral</td>
<td>3 ds linear, 4 kb</td>
<td>V</td>
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</tbody>
</table>
DNA Virus Families

1. Poxviruses
   (named after Small Pox virus which is in this group), vaccinia (small pox vaccine virus), monkey pox (HSV1, HSV2, Cytomegalovirus, Epstein-Barr virus, KSHV)

2. Herpesviruses

3. Adenoviruses
   (first isolated from adenoid tissue) adenovirus
   (named for 3 major members of family: Papilloma [warts, cervical carcinoma], polyoma [multiple tumors], vacuolating agent [SV40])
   (Hepa = liver, dna = DNA), Hepatitis B (small), B19

4. Papovaviruses

5. Hepadnaviruses

6. Parvoviruses

*nonenveloped
<table>
<thead>
<tr>
<th>Family</th>
<th>Nucleocapsid morphology</th>
<th>Envelope</th>
<th>Virion morphology</th>
<th>Genome</th>
<th>Host</th>
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</thead>
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<td><strong>dsDNA viruses</strong></td>
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<td>Alloherpesviridae</td>
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<td>Spherical, tegument</td>
<td>2 ds linear, 135–294 kb</td>
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<td>Asfarviridae</td>
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<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Icosahedral</td>
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<td>V, I</td>
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<td>Herpesviridae</td>
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<td>Spherical, tegument</td>
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<td>Iridoviridae</td>
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<td>Icosahedral</td>
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<td>V, I</td>
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<tr>
<td>Papillomaviridae</td>
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<td>Icosahedral</td>
<td>1 ds circular, 7–8 kb</td>
<td>V</td>
</tr>
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<td>Polyomaviridae</td>
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<td>Icosahedral</td>
<td>1 ds circular, 5 kb</td>
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<td>Poxviridae</td>
<td>Ovoid</td>
<td>Yes</td>
<td>Ovoid</td>
<td>1 ds linear, 130–375 kb</td>
<td>V, I</td>
</tr>
<tr>
<td><strong>ssDNA viruses</strong></td>
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</tr>
<tr>
<td>Anellovirus</td>
<td>Icosahedral</td>
<td>No</td>
<td>Icosahedral</td>
<td>1 – circular, 2–4 kb</td>
<td>V</td>
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<td>Circoviridae</td>
<td>Icosahedral</td>
<td>No</td>
<td>Icosahedral</td>
<td>1 – or ± circular, 2 kb</td>
<td>V</td>
</tr>
<tr>
<td>Parvoviridae</td>
<td>Icosahedral</td>
<td>No</td>
<td>Icosahedral</td>
<td>1 +, – or ± linear, 4–6 kb</td>
<td>V, I</td>
</tr>
<tr>
<td><strong>dsDNA reverse transcribing viruses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepadnaviridae</td>
<td>Icosahedral</td>
<td>Yes</td>
<td>Spherical</td>
<td>1 ds circular, 3–4 kb</td>
<td>V</td>
</tr>
</tbody>
</table>
Importance of Virion Structure and Classification

1. Stability--enveloped vs nonenveloped
2. Mechanisms of Virus Entry into Cells
3. Mechanisms of Virus Replication
4. Mechanisms of Virus Assembly--virus spread
5. Nucleic Acid--Oncogenic Potential
6. Nucleic Acid-Genetic Stability
7. Virus Classification--helps in understanding/controlling virus infections   Examples--hantavirus, SARS
Details of Virus Structure

Nonenveloped

Enveloped
STRUCTURE OF NONENVELOPED VIRUSES

Capsid---icosahedron
- 20 faces--each icosahedral triangle
- 12 vertices
- Repeating subunits (capsomeres)
- Simplest= 60 capsomeres

Example--Picornaviruses
- simple-60 capsomeres
- capsomere=VP1, VP2, VP3, VP4

Example--Adenovirus
- much more complex
- Hexons, pentons (base, fiber, knob)
  - hexon capsomere=3 hexons
  - 180 capsomeres
  - 12 pentons (one at each vertex)

Example--reoviruses multiple capsids (shell within a shell)
Icosahedral structure of capsids

edges

vertices

faces

2-fold symmetry

3-fold symmetry

5-fold symmetry
Picornavirus Structure

Example of a simple, non-enveloped virus
Picornaviruses  (small, RNA)

**Rhinoviruses**---over 100 serotypes

**Enteroviruses**
- polioviruses  3 serotypes
- Coxsackie viruses  many serotypes
- Echoviruses  many serotypes
- Enteroviruses  several serotypes

**Aphthoviruses** (FMDV)

**Cardioviruses** (mice)

**Hepatoviruses**--Hepatitis A
Picornavirus Structure

Capsomere=VP1, VP2, VP3, VP4

Virion  60 capsomeres

RNA 7.5 kb
coding capacity??

single stranded

positive polarity
Rhinovirus 14

VP1=blue
VP2=green
VP3=red

VP4 inside
Cut away
Inside
VP4--yellow
Enveloped Virus Structure

Membrane:

- Spikes--glycoproteins
- Membrane or matrix protein (some)
- Lipid Bilayer

Core:

- Capsid=icosahedron
  - eg flaviviruses, herpesviruses
  - or
- Nucleocapsid=helical structure
  - eg. Influenza, paramyxoviruses
Enveloped Virus Structure

- Glycoproteins
- Helical nucleocapsid
- Icosahedral capsid
- Genome
- Lipid bilayer
- Lymphoid capsid
Enveloped virus with capsid core
example togavirus
Enveloped Virus with Helical Core

Intact virion
Disrupted virion

Helical nucleocapsid
(inside envelope)
Influenza—Structure

Enveloped
Negative-stranded, RNA Genome
Segmented Genome ***
Influenza virus
Envelope

Lipid Bilayer--membrane

Four Proteins

HA--hemagglutinin
NA--neuraminidase
M1--matrix
M2--ion channel
Hemagglutinin--HA

Attachment to cell receptors
sialic acid

Membrane Fusion--entry

Target of neutralizing antibody

Determinant of Organ Tropism--cleavage site
HA0 cleaved to HA1 + HA2
Neuraminidase--NA

Cleaves sialic acid from glycoproteins and glycolipids

Important role in virus release

Target of antiviral drugs
M2

Small hydrophobic protein

Role in virus entry

Ion channel

M1

Lines inner surface of membrane

Structural connection of envelope with core

Important in virus classification
Distributions and shape-based differentiation of HA and NA spikes (cryo EM)

Influenza Virus Core

RNA genome
  8 segments of negative stranded RNA

Associated Proteins
  NP (structural)
  PA, PB1, PB2 (virion associated polymerase)
Central slices through influenza virions containing \((7 + 1)\) solenoid-like RNP configurations

Organization of Genome in Influenza Virions
Note Segmented Genome—Each segment codes for one (or two) proteins

Summary of Influenza virus Structure
## Classification of Influenza Viruses

<table>
<thead>
<tr>
<th></th>
<th>Classification</th>
<th>Host Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Pandemics</td>
<td>broad host range humans, pigs, birds, seals</td>
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<tr>
<td>B</td>
<td>Epidemics</td>
<td>humans only</td>
</tr>
<tr>
<td></td>
<td>No pandemics</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Endemic</td>
<td>humans only</td>
</tr>
</tbody>
</table>

Important for epidemiology (and vaccination)

Classification based on NP and M proteins
Further Classification of Influenza A Viruses

Divided into subtypes or species

Based on HA and NA

In nature 17 different HA genes (H1—H17)
9 different NA genes (N1-N9)
Subtypes designated by which HA and which NA are present
eg. H1N1 or H3N2

All exist in wild birds (H17, bats)

Each subtype has many antigenic variants
Unique Epidemiology of Influenza:

1. Periodic Epidemics (regional) (seasonal flu)
2. Periodic Pandemics (world wide epidemics) (pandemic flu)

<table>
<thead>
<tr>
<th>Early Pandemics?</th>
<th>Documented Pandemics</th>
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<tr>
<td>1761-62</td>
<td>1890</td>
</tr>
<tr>
<td></td>
<td>1900</td>
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<tr>
<td>1833-37</td>
<td>1918</td>
</tr>
<tr>
<td></td>
<td>20-50 million deaths world wide</td>
</tr>
<tr>
<td></td>
<td>675,000 deaths in US</td>
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<tr>
<td></td>
<td>1957</td>
</tr>
<tr>
<td></td>
<td>1968</td>
</tr>
<tr>
<td></td>
<td>(1977)</td>
</tr>
<tr>
<td></td>
<td>2009</td>
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</table>
Influenza A and Pandemics

(pandemics caused by new subtype)

1890  H2N2
1900  H3N8
1918  H1N1  Antigenic Shift
1957  H2N2
1968  H3N2
2009  H1N1

(Discuss H5N1, H7,N9 viruses)
Classification of Influenza B Viruses

No subtypes--same HA and NA

Many antigenic variants
Infection of Cells

1. **Encounter**--Virus in proximity of susceptible cells

2. **Attachment**--Virus Binding to Cell Surfaces

3. **Entry**--Insertion of Viral Genome into cells

4. **Replication**--Synthesis of components of Virions

5. **Assembly**--formation of progeny virions

6. **Release**--release of progeny virus from infected cells
Encounter

Nonspecific (random) for all viruses
Encounter: Picornaviruses vs Influenza viruses
Attachment

Specific Interaction

VAP (virus attachment protein)
  nonenveloped—a capsid protein (Picornavirus—VP1)
  enveloped—a spike (glycoprotein) (Influenza virus—HA)

Cell Receptor (specific to virus)—distribution determines (in part):
  species specificity of virus infection
  organ specificity of virus infection
Virus-Receptor interactions---virus specific interaction
How are VAPs identified?

1. Antibodies
2. Mutation
3. Soluble protein

Picornavirus VAP=VP1

Influenza VAP=HA (hemagglutinin)
Examples of Receptors

Picornaviruses
  rhinoviruses  ICAM1 (most rhinoviruses)
  polio virus  PVR (CD155)
  Coxsackie  CAR  DAF (not sufficient)
### TABLE 16.3 Some Cell Receptors for Picornaviruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virus receptor</th>
<th>Type of receptor</th>
<th>Coreceptor</th>
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<tbody>
<tr>
<td><strong>Aphthovirus</strong></td>
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<td></td>
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<tr>
<td>Foot-and-mouth disease virus</td>
<td>Heparan sulfate</td>
<td>Glycosaminoglycan</td>
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<tr>
<td>(cell culture adapted)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Foot-and-mouth disease virus</td>
<td>α,β1, α,β2, α,β3, α,β4, α,β5</td>
<td>Integrin</td>
<td>Carbohydrate</td>
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<tr>
<td>Equine rhinitis A virus</td>
<td>Sialic acid</td>
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<tr>
<td><strong>Cardiovirus</strong></td>
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<tr>
<td>Encephalomyocarditis virus</td>
<td>Vcam-1</td>
<td>Ig-like</td>
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<td>Theiler’s murine</td>
<td>Sialylated glycoconhirin A for hemagglutination only</td>
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<td>encephalomyelitis virus</td>
<td>Sialic acid</td>
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<td>Low neurovirulence strains</td>
<td>Sialic acid</td>
<td>Carbohydrate</td>
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<tr>
<td>High neurovirulence strains</td>
<td>Heparin sulfate</td>
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<tr>
<td><strong>Enterovirus</strong></td>
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<tr>
<td>Bovine enterovirus</td>
<td>Sialic acid</td>
<td>Carbohydrate</td>
<td>β1-Microglobulin, GRP78, MHC-1</td>
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<tr>
<td>Coxsackievirus A9</td>
<td>α,β1, α,β2</td>
<td>Integrin</td>
<td></td>
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<tr>
<td>Coxsackievirus A13, A18, A21</td>
<td>Icam-1 (CD)</td>
<td>Ig-like</td>
<td></td>
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<tr>
<td>Coxsackievirus A16</td>
<td>P-selectin glycoprotein ligand-1 (PSGL-1), scavenger receptor class B (SCARB2)</td>
<td>Mucin-like</td>
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<td>Coxsackievirus A21</td>
<td>Decay-accelerating factor (C055)</td>
<td>SCR-like (complement</td>
<td>Icam-1</td>
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<td></td>
<td></td>
<td>cascade</td>
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<tr>
<td>Coxsackievirus A24</td>
<td>Sialic-acid containing O-linked glycoconjugates</td>
<td>Carbohydrate</td>
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<tr>
<td>Coxsackievirus B1–B6</td>
<td>Car (coxsackievirus-adenovirus receptor)</td>
<td>Ig-like</td>
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<tr>
<td>Coxsackievirus B1, B3, B5</td>
<td>Decay-accelerating factor (C055)</td>
<td>SCR-like (complement</td>
<td>α,β2-Integrin (C0B)</td>
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<tr>
<td></td>
<td></td>
<td>cascade</td>
<td>CAR (C0B3)</td>
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<td>β1-Microglobulin,</td>
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<td>CD58 (E7)</td>
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<td>Echovirus 1, 8</td>
<td>α,β1-Integrin (Vla-2)</td>
<td>Integrin</td>
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<td>Echovirus 3, 5, 7, 11–13, 20,</td>
<td>Decay-accelerating factor (C055)</td>
<td>SCR-like (complement</td>
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<td>21, 24, 29, 30, 33</td>
<td>Heparan sulfate</td>
<td>cascade</td>
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<td>Echovirus 5</td>
<td>α,β1-Integrin</td>
<td>Integrin</td>
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<td>Echovirus 9</td>
<td>Decay-accelerating factor (C055) sialic acid</td>
<td>SCR-like (complement</td>
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<td></td>
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<td>carbohydrate</td>
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<td>Enteroxivirus 70</td>
<td>Icam-1 (PSGL-1), scavenger receptor class B (SCARB2)</td>
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<tr>
<td>Enteroxivirus 71</td>
<td>P-selectin glycoprotein ligand-1 (PSGL-1), scavenger receptor class B (SCARB2)</td>
<td>Ig-like</td>
<td></td>
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<tr>
<td>Parechovirus 1</td>
<td>α,β1, α,β3</td>
<td>Integrin</td>
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<tr>
<td>Parechovirus 1</td>
<td>α,β1, α,β3 (Vitonectin receptor)</td>
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<td>Hepatitis A virus</td>
<td>HAVcr-1</td>
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<td>Polioviruses 1–3</td>
<td>Pvr (CD155)</td>
<td>T-cell Ig-like,</td>
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<tr>
<td>Rhinoviruses (major group,</td>
<td>Icam-1</td>
<td>mucin-like (TIM)</td>
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<tr>
<td>91 serotypes)</td>
<td></td>
<td>Ig-like</td>
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<tr>
<td>Rhinoviruses (minor group,</td>
<td>Low-density lipoprotein receptor protein family</td>
<td>Signaling receptor</td>
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<tr>
<td>10 serotypes)</td>
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</tbody>
</table>

Ig, Immunoglobulin; SCR, short consensus repeat.
Importance of Receptors

Determinant of Species Specificity
example  polio virus (CD155—primate only)

influenza A
  2,3 linkage (avian) vs 2,6 linkage (human)

of sialic acid

Determinant of Organ specificity
example  HIV --CD4 expressing cells
How are receptors identified?

Essential tool: permissive and nonpermissive cells (cell line expressing the receptor and cells not expressing the receptor)  How identify??

1\textsuperscript{st} step in identifying potential receptors—ID potential candidates—Methods?

Then, Verify.

Tools:  
1. Antibodies  
2. cDNAs of candidates  
3. Soluble proteins  
4. Inhibition of expression

Complications: co-receptors, attachment factors
Proof of that a receptor candidate is a receptor

1. Expression of candidate in permissive cells but not resistant cells

2. Transfection of resistant cells with vector expressing the candidate converts cells to permissive cells

3. Inhibition of expression of receptor candidate blocks virus infection/binding of virus

4. Direct interaction between VAP and receptor candidate

5. Soluble receptor competes with cells for virus binding
VAP-receptor Interactions

A. Species and organ specificity

B. VAP and Neutralizing antibody (definition)

C. Neutralizing antibody binding vs receptor binding definition of serotype
Virus--antibody complexes

Neutralizing Antibody blocks attachment
Serotype--defined by neutralizing antibody

Virus A + anti-A  
Virus B+anti-B  
Virus A+anti-B

No infection  
No infection  
Infection

All viruses inhibited by anti-A are same serotype (serotype A)

All viruses inhibited by anti-B are the same serotype (serotype B) which is different from serotype A
Implications of Different Serotypes of a Virus

1. Significant variability on the surfaces of virions

2. Infection due to one serotype will not protect against subsequent infection with another serotype

   For example, individuals may be infected with rhinoviruses many times since there are multiple serotypes of this virus

   What does this mean structurally??
Rhinovirus 14

VP1=blue
VP2=green
VP3=red

VP4 inside
Poliovirus

Depth cued

VP1
Soluble ICAM1 bound to rhinovirus 14
Virus-receptor Interactions

Attachment to cell receptors
Rhinovirus 14
antigenic sites in pink (sites of Ab binding)
Virus-Neutralizing Antibody Interactions

Attachment to cell receptors

Ab neutralization

Ab blocks cell receptor-virion interactions
Evidence for Site of Antibody Binding/
Antibody Neutralization

Antibody escape mutants

Directed mutations

Crystallography
Influenza Virus-Receptor Interactions

Hemagglutinin--HA is VAP

Attachment to cell receptors
sialic acid

Target of neutralizing antibody

Determinant of Organ Tropism--cleavage site
HA0 cleaved to HA1 +HA2

Membrane Fusion--entry
HA of four different subtypes of Influenza (trimer of HA)

Sialic acid binding Site in blue
Neutralizing Ab (green) bound to HA trimer (blue and red)
Influenza HA

Monomer

Receptor binding site
Globular head
Stalk
Fusion peptide
Bromelain cleavage site

Monomer

Antigenic sites
Helix B
Helix A
Fusion peptide

trimer

Antibody binding sites vs sialic acid binding site
Antigenic Drift

Antigenic variants of one subtype

Cause of epidemics (not pandemics)
Antigenic Drift

Neutralizing antibody binding sites

Amino acid change in each of five sites (a-d) = Antigenic variant (drift)
Pandemics Due to Antigenic Shift

(completely new HA introduced into human population)

Mechanism will be defined in Lectures 4 and 5
Reading

**Fields Virology (edition 5)**

Chapters 2, 3 (pages 59-82), and 4 (pages 99-105)

Chapters 24 (pages 796-808), 47 (pages 1647-1653)