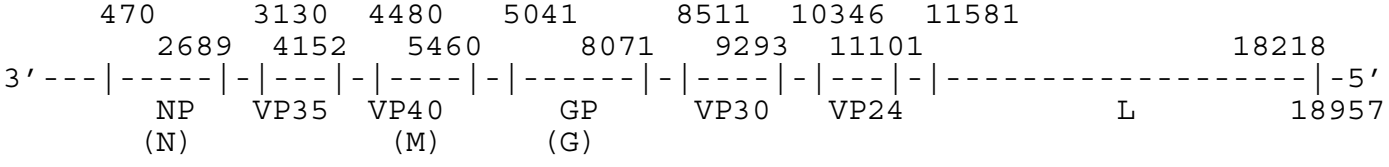
THE EMERGING VIRUSES

VIRUS FAMILY: **FILOVIRIDAE** (Filo = Threadlike)

I. DISTINGUISHING CHARACTERISTICS
- A. Enveloped, negative, ss RNA, linear [MONONEGAVIRALES]
- B. Virions are pleomorphic : long filamentous,branched or 'U'-shaped, 'b'-shaped or circular forms
- C. mRNAs made by unique mechanism in order of genome
- D. Replication and "Transcription" of genome separate
- E. Envelope derived from host plasma membrane
- F. Cause severe, often fatal hemorrhagic fever - Includes Ebola and Marburg viruses, **"EMERGING VIRUSES"**

II. STRUCTURE (Based on Ebola, strain Zaire - "Mayinga"
- A. SIZE: ~80 nm in diameter, particles vary in Length (up to 14,000 nm): Ebola virus-805 nm ; Marburg virus-665 nm
- B. ENVELOPE: YES, Derived from host plasma membrane; Spikes of 7 nm length visible on the virion surface.
  1. GLYCOPROTEINS: GP 74 kD, Cleaved to GP1-GP2.
  2. OTHER PROTEINS: sGP Made without editing from GP gene [GP is made by an addition of A at editing site, 6918.]
     ssGP Made by deleting an A at 6918.
  3. MATRIX PROTEIN: VP40
- C. NUCLEOCAPSID : Helical
  1. NUCLEIC ACID
     - a. TYPE: RNA BALTIMORE TYPE: V
     - b. STRANDED: ss, linear, non-segmented
     - c. POLARITY: negative
     - d. MOL. WT.: 4.2×10^6, ~19000 nts.
     - e. # GENES: 7
     - f. SEQUENCE: GENBANK AN: AF086833
  2. GENETIC (PHYSICAL) MAP:



  3. CAPSID
     - a. SYMMETRY: Helical
     - b. CAPSOMERS: NP 74kD

OTHER PROTEINS	MW (EBOLA)	FUNCTION
L-Protein	243kD	REPLICASE
VP 30	30kD	MINOR NP
VP 35	35kD	REPLICASE ASSOC.
VP 40	40kD	MATRIX PROTEIN
VP 24	24kD	MEMBRANE ASSOC.?

VIRUS FAMILY: **FILOVIRIDAE**

III. CLASSIFICATION AND CHARACTERISTIC MEMBERS

GENUS	MEMBERS
FILOVIRUS	EBOLA VIRUS
	MARBURG VIRUS

IV. VIRAL MULTIPLICATION

A. ABSORPTION: The mechanism of virus entry into host cells is unknown but probably the transmembrane protein (GP) mediates the adsorption and penetration process.

B. PENETRATION: Same as above

C. UNCOATING: Not known

D. GENE EXPRESSION: Takes place in the cytoplasm of infected cells. The 3'UTR of the genome probably provides the encapsidation site for the nucleoprotein as well as the entry site for the polymerase. The genome is transcribed to yield monocistronic mRNAs that are complementary to the viral genomic RNA. The 5'ends of the subgenomic RNAs start at the transcription start signal sequence, GAUGAAGAUUA, and the 3' ends carry a poly(A) tail generated by the polymerase at a run of uridine residues located at the 5'ends of all transcription termination signal sequences, AUUAAGAAAAA [Sequences are for + strand.]. A special feature of GP gene transcription is the generation of three different mRNAs due to an editing site at position 6918-6924. Direct transcription followed by translation results in sGP a small GP. Addition of one A (in the run of As) results in a frameshift in translation and production of GP. Addition of two As (or deletion of one A) results in another frameshift and production of ssGP.

E. REPLICATION: Is mediated by the synthesis of full length complementary antigenome(+sense) which then serves as the template for the synthesis of progeny negative-strand RNA.

F. ASSEMBLY : As infection proceeds, the filaments grow and become highly structured.

G. BUDDING AND/OR RELEASE : Budding takes place at cell membrane sites which are altered by insertion of the viral glycoprotein and alignment of viral membrane-associated proteins as well as of preformed nucleocapsids.

V. CLINICAL CORRELATIONS: Marburg and Ebola viruses are termed "**EMERGING VIRUSES**" which refers to viruses that have newly appeared or are rapidly expanding their range with a corresponding increase in cases of disease.

Host Range and Virus Distribution: The natural reservoirs for human infections with Marburg and both subtypes of Ebola viruses and the natural source of Reston virus are unknown. Human infections with Reston virus have been documented during the

1989 epizootic. Experimental hosts include monkeys for which infection with Marburg and Ebola-Zaire virus are usually lethal, whereas some animals survive Ebola-Sudan virus infection. Reston virus infection of monkeys showed that this filovirus is less pathogenic for primates than Marburg virus and both subtypes of Ebola virus.

Transmission and Tissue Tropism: The mode of primary infection in natural settings is unknown. All secondary cases have been nosocomial or caused by intimate contact with a patient, transmission usually by contaminated blood samples.

Pathogenicity: Marburg and Ebola viruses cause severe hemorrhagic fever in humans and laboratory primates. According to the evidence present to date, Reston virus may also cause hemorrhagic fever in monkeys, but appears to be apathogenic for humans. In man, the Zaire strain of Ebola virus apparently carries the highest mortality when compared with the Sudan strain or Marburg virus, although it is not clear to what extent these differences depend on the mode of transmission.

Clinical Features of Infection: Clinical symptoms are similar with Marburg and Ebola virus infections. Following incubation periods of 4-16 days, onset is sudden, marked by fever, chills, headache, anorexia and myalgia. These signs are soon followed by nausea, vomiting, sore throat, abdominal pain and diarrhea. When first examined, patients are usually overtly ill, dehydrated, apathetic and disoriented. Pharyngeal and conjunctival infections are usual. Most of the patients develop severe hemorrhagic manifestations, usually between days 5 and 7. Bleeding is often from multiple sites, with the gastrointestinal tract, lungs and gingiva the most commonly involved. Bleeding and oropharyngeal lesions usually herald a fatal outcome. Death occurs between day 7 and 16, usually from shock with or without severe blood loss.

Pathology and Histopathology: Marburg and Ebola viruses cause similar pathological changes in man. The most striking lesions are found in liver, spleen and kidney. These lesions are characterized by focal hepatic necrosis with little inflammatory response and by follicular necrosis of lymph nodes and spleen. In late stages of the disease, hemorrhage occurs in the gastrointestinal tract, pleural, pericardial and peritoneal spaces and into the renal tubules with deposition of fibrin.

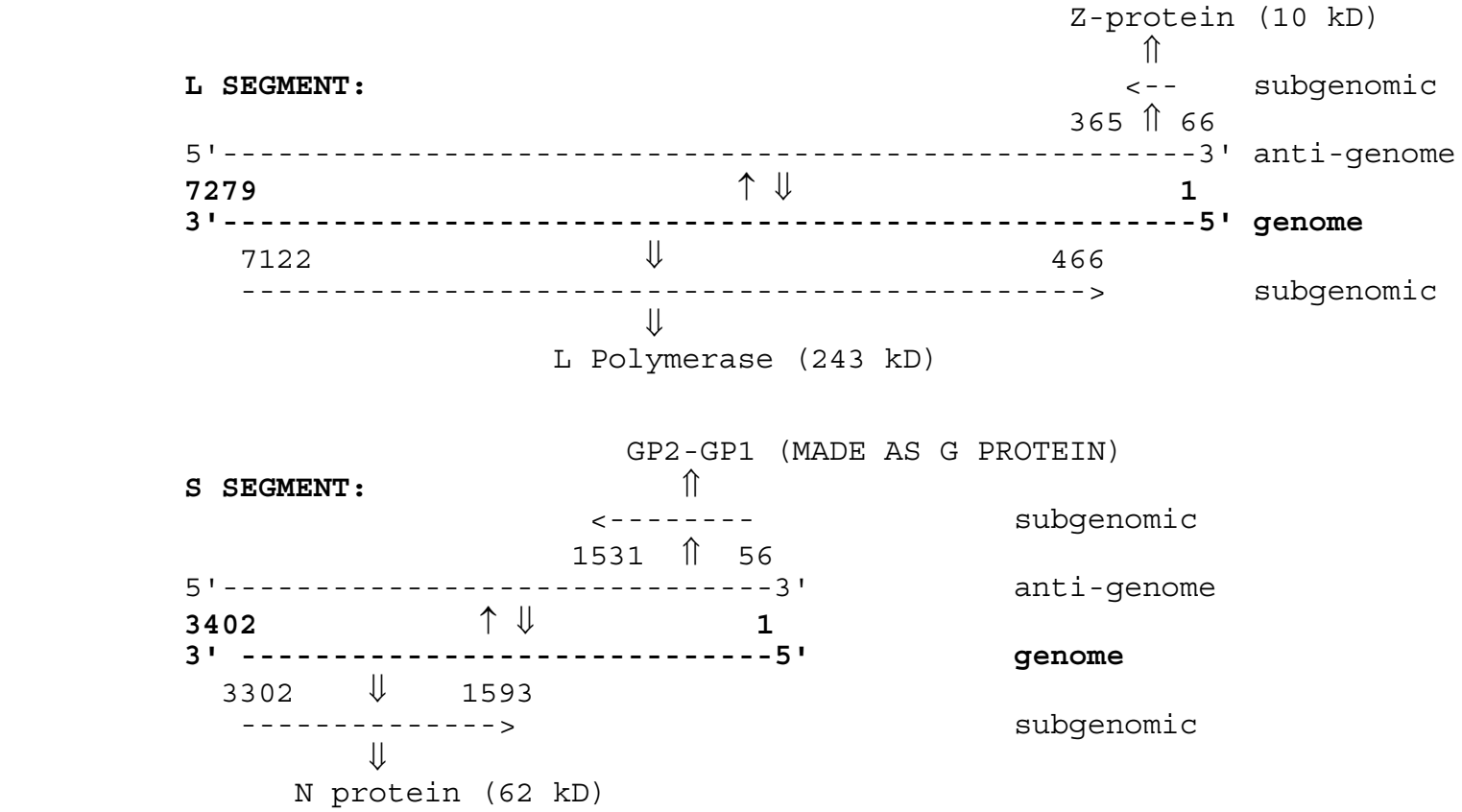
Immune Response: Humoral immune response to Marburg and Ebola viruses can be detected as early as 10-14 days after infection. Antibodies are directed primarily against the surface glycoproteins. Owing to the unreliability of neutralization tests, little can be said about their protective effects. Little is known also about the cell-mediated immune response to these viruses.

VIRUS FAMILY: **ARENAVIRIDAE** (Arena=sand)

I. <u>DISTINGUISHING CHARACTERISTICS</u>

A. SPHERICAL, ENVELOPED WITH GLYCOPROTEIN PEPLOMERS
B. GENOME IN 2 SINGLE-STRANDED, AMBISENSE SEGMENTS
C. RIBOSOMES PACKAGED INSIDE ENVELOPE (SAND IN EM)
D. MEMBERS INFECT MAN VIA RODENTS
E. CAUSE RASH/HEMORRHAGIC-FEVERS
F. LASSA FEVER V WAS ONE OF THE FIRST "EMERGING VIRUSES"

II. STRUCTURE (BASED ON LASSA VIRUS, JOSIAH STRAIN)
A. SIZE: 100 - 130 nm in dia.
B. ENVELOPE: PRESENT - BUDS THROUGH PLASMA MEMBRANE
1. GLYCOPROTEINS: GP1 (42kD) SPIKE (TETRAMER)
GP2 (34kD) TRANSMEMBRANE
2. MATRIX PROTEIN: NONE
C. NUCLEOCAPSID
1. NUCLEIC ACID
a. TYPE: RNA BALTIMORE TYPE: V
b. STRANDED: SS
c. POLARITY: AMBISENSE IN BOTH L AND S
d. MOL. WT.: L (7279 b) S (3402 b)
e. SEQ.-GENBANK AN: L(NC 004297), S(NC 004296)
f. # GENES: 5 #ORFS: 2 ON GENOME, 2 ON ANTIGENOME
g. TERMINAL BASE-PAIRING REGIONS OF ~20 BP
2. GENETIC (PHYSICAL) MAP:



VIRUS FAMILY: **ARENAVIRIDAE**
3. CAPSID
a. SYMMETRY: HELICAL
b. SIZE: 2 X >100 run
c. CAPSOMERS: N PROTEIN, 62 KD

d. COMPOSITION:

PROTEIN	MW (KD)	COPY NO.	FUNCTION
N	62	>1000	NUCLEOPROTEIN
L	243	>10	REPLICASE
Z	10	?	ZN-BINDING PROTEIN (?)

III. CLASSIFICATION AND CHARACTERISTIC MEMBERS

GENERA	PROPERTIES	MEMBERS
ARENAVIRUS	RODENT-RESERVOIRS	LCM IS TYPE VIRUS
	2 SEROGROUPS:	
	OLD WORLD	LASSA, MOBALA
	NEW WORLD	TACARIBE, JUNIN, MACHUPO, PICHINDE

IV. VIRAL MULTIPLICATION

A. **ABSORPTION & PENETRATION:** GI protein binds the virus to cell receptor. Endocytosis brings the virus into the cytoplasm and also strips the envelope.

B. **UNCOATING**: Uncoating of the N/RNA is not complete and N protein seems to be required for both "transcription" and RNA replication. Both are catalyzed by protein L.

C. **GENE EXPRESSION:** The virus is ambisense in both its RNA segments, and subgenomic mRNAs are "transcribed from both the genome and the antigenome strands. The first 10 nucleotides plus the cap of host mRNAs are "cannibalized" to provide primers for "transcription" of the two genome segments. L mRNA is transcribed from the 3'-end of the L genomic strand resulting in a large mRNA which is translated into the L-protein. From the 3'-end of the full-length antigenome L strand another subgenomic mRNA is made which codes for the Z-protein. The S RNA genomic strand is also ambisense, and an mRNA (again primed by host-capped nucleotides) is made from its 3'-end and codes for the 62kd N-protein. The antigenome strand is transcribed into another small mRNA that codes for the two Glycoproteins, GP1 and GP2 that are cleaved from a precursor glycoprotein (the G-protein).

D. **GENOME REPLICATION**: The genome is replicated from full-length genome strands which are replicated separately from the mRNA pools. Full-length antigenome strands (vc strands) are made from the genome strand templates. Both reactions are catalyzed by the polymerase, protein L.

E. **ASSEMBLY:** N coats the new viral genomes and they circularize due to their complementary ends (panhandles). The two genome segments (via the N protein ??) interact with the cytosolic domain of GP2, the transmembrane glycoprotein.

F. **BUDDING AND/OR RELEASE:** The two nucleoprotein genome segments aggregate and bud through the plasma membrane. The process is not exact and often multiple copies of the genome and even nearby ribosomes are enclosed in the budding virion. The viral patch is made up of GP2 transmembrane protein bound to a tetrameric, globular GP1 spike protein.

V. CLINICAL CORRELATIONS

A. Lassa fever was first recognized due to an outbreak in Lassa, Nigeria, in 1969. A nurse contracted the disease from a patient in a small hospital and several other hospital workers were also infected. One nurse was evacuated to the US where she recovered, but during the viral isolation at Yale University two others became infected and one died of Lassa Fever. The virus is now known to be endemic in rural West Africa. Its reservoir host is the native mouse, *Mastomys natalensis*. Several outbreaks have occurred since 1969 in both rural and urban settings. All have had disease rates of ~20% and a case mortality rate of ~15%. Millions of West Africans have antibody to the virus, and each year about 2000 die of Lassa Fever.

B. The first known (isolated) Arenavirus was LCM, Lymphocytic Choriomenigitis Virus. This virus infects the common house mouse, *Mus musculus*, without disease, and occasionally infects man. Human infections are often without disease but in some an influenza-like illness develops. Rarely a more serious meningitis or encephalitis is seen.

C. The New World viruses cause three South American hemorrhagic fevers: Argentine (Junin virus), Bolivian (Machupo virus) and Venezuelan (Guanarito virus). All of these diseases are enzootic and man is infected because of close contact with the rodent host. For example the spread of Junin virus to man was probably due to the widespread planting of maize and with it the proliferation of the vole host, *Calomys musculinus*. Symptoms include hemorrhage, thrombocytopenia, leucopenia, hypotension and death results from hypovolemic shock. The most recent outbreak is Venezuelan HF. The virus is enzootic in the cotton rat, *Sigmodon hispidus*. Household contact with rodents seems to be the mode of transmission (due to contaminated urine and droppings).