Flavivirus

Flaviviridae

EDWIN G. WESTAWAY

Kunjin virus. Negative stain. Length of bar [nm]: 50 [previously unpublished by E. G. Westaway]

Virion

Morphology spherical, possibly icosahedral
Envelope yes
Diameter [nm] 45-50
Length [nm] n/a
Structural components . . . core particle enclosed in envelope (a lipid bilayer)
Buoyant density [g/mL] . . 1.22-1.24
Additional information . . . sediments at about 200S; spikes appear on virion at low pH

Genome

Nucleic acid RNA
Strandedness single-stranded
Polarity positive-sense
Configuration linear
Segments 1
Size [kb] 11
G+C content [%] 48
Transcription units 1
Additional information . . . 5' cap; gene order C-prM-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5; no poly(A) tail; conserved 5' and 3'-terminal stem loops

Replication Strategy

Entry mechanism receptor-mediated endocytosis, fusion with endosomal membrane
Site of transcription cytoplasm
Transcriptase viral replicase copies RNA(+) into full length RNA(-)
Site of genome replication . . induced membranes (vesicle packets) in cytoplasm
Replicase virus-encoded RNA-dependent RNA polymerase (NS5)
Replication intermediate . . double-stranded RNA with nascent RNA (+) strand
Site of virion assembly . . . in endoplasmic reticulum and accumulation in vesicles
Egress mechanism cytoplasmic vesicles released by exocytosis (budding rarely observed)
Additional information . . . the single open reading frame of genomic RNA is translated as a polyprotein, co- and post-translationally cleaved by cell signal peptidase and at dibasic sites by the viral protease; replicase complex: NS1, NS2A, NS3, NS4A, NS5

History

Year	Event	Reference
1900	Transmission of yellow fever by mosquitoes	Reed W, Carroll J (1902) Amer Med 3:301-305
1959	Infectious RNA extracted from virions (Murray Valley encephalitis virus)	Anderson SG, Ada GL (1959) Aust J Exptl Biol Med Sci 37:353-364
1960	Dengue virus associated with dengue haemorrhagic fever	Hammon WMCD, et al. (1960) Science 131:1102-1103
1968	IgM has greater specificity than IgG antibody in flavivirus hemagglutination-inhibition tests	Westaway EG (1968) Nature 219:78 -79
1968	Electron microscopy of membranes induced in cells during flavivirus infections	Murphy FA, et al. (1968) Lab Invest 19:656-662
1969	Flavivirus structural proteins first defined (dengue type 2, Kunjin viruses)	Stollar V (1969) Virology 39:426-438; Westaway EG, Reedman BM (1969) J Virol 4:688-693
1970	Dengue haemorrhagic fever associated with dengue serotype cross reactive antibodies	Halstead SB, et al. (1970) Yale J Biol Med 42:311-328
1977	All virus-specified proteins recognized in cell lysates were unrelated (Kunjin virus)	Wright PJ, et al. (1977) J Virol 24:651-661; Wright PJ, Westaway EG (1977) J Virol 24:662-672
1977	Absence of subgenomic RNA in infected cells (Kunjin virus)	Boulton RW, Westaway EG (1977) Arch Virol 55:201-208
1981	Replicative intermediate (RI) and replicative form (RF) RNAs identified (dengue type 2 virus)	Cleaves GR, et al. (1981) Virology 111:73-83
1985	RF identified as recycling template for asymmetric semi-conservative RNA synthesis (Kunjin virus)	Chu PWG, Westaway EG (1985) Virology 140:68-79
1985	New virus family Flaviviridae created	Westaway EG, et al. (1985) Intervirology 24:183-192
1985	Nucleotide sequence of the yellow fever virus genome, the gene order and predicted 3'-terminal stem loop	Rice CM, et al. (1985) Science 229:726-733
1986	Evidence that an acidic environment promotes rapid uncoating of cell-associated West Nile virus	Gollins SW, Porterfield JS (1986) J Gen Virol 67:1941-1950
1988	Translation strategy defining all correct cleavages in the polyprotein (Kunjin virus)	Coia G, et al. (1988) J Gen Virol 69:1-21; Speight G, et al. (1988) ibid 69:23-34
1988	Characteristic 5'-terminal stem loop structure predicted for several flaviviruses	Brinton MA, Dispoto JH (1988) Virology 162:290-299
1989	Antigenic structure of envelope protein at the molecular level (tick-borne encephalitis virus)	Mandl CW, et al. (1989) J Virol 63:560-571
1989	Infectious yellow fever virus RNA transcribed from ligated cDNA	Rice CM, et al. (1989) New Biologist 1:285-296
1990	Role of N-terminal domain of NS3 established as serine protease cleaving viral polyprotein at dibasic sites	Preugschat F, et al. (1990) J Virol 64:4364-4374; Chambers TJ, et al. (1990) Proc Natl Acad Sci USA 87:8898-8902

Year	Event	Reference
1991	NS3 serine protease and co-factor NS2B are required for cleavages at dibasic sites in the viral polyprotein	Falgout BJ, et al (1991) J Virol 65:2467-2475; Chambers TJ, et al. (1991) ibid 65:6042-6050
1992	Active replicase complex purified with induced membranes and separated from structural proteins (Kunjin virus)	Chu PWG, Westaway EG (1992) Arch Virol 125:177-191
1993	Carboxy terminal domains of NS3 contain NTPase and RNA triphosphatase activities (West Nile virus)	Wengler G, Wengler G (1991) Virology 184:707-715; Wengler G, Wengler G (1993) Virology 197:265-273
1995	Crystal structure solved for envelope protein (tick-borne encephalitis virus)	Rey F, et al. (1995) Nature 375:291-298
1996	NS5 shown to copy RNA non-specifically in vitro (dengue type 1 virus)	Tan B-H, et al. (1996) Virology 216:317-325
1996	Putative sites of viral RNA synthesis and protease activities identified by cryo-immuno-electron microscopy	Mackenzie JM, et al. (1996) Virology 220:232-240; Westaway EG, et al. (1997) J Virol 72:823-829
1997	Subgenomic non-cytopathic self-replicating RNA (Kunjin virus replicon)	Khromykh AA, Westaway EG (1997) J Virol 71:1497-1505
1998	Apoptosis in the mouse central nervous system during infection with dengue viruses	Despres P, et al. (1998) J Virol 72:823-829
1998	Consensus composition of the replicase complex: NS1, NS2A, NS3, NS4A, NS5 with dsRNA (Kunjin virus)	Mackenzie JM, et al. (1998) Virology 245:203-215
1999	Crystal structure solved for NS3 protease domain (dengue type 2 virus)	Murthy MHK, et al. (1999) J Biol Chem 274:5573-5580; Brinkworth RI, et al. (1999) J Gen Virol 80:1167-1177
1999	Helicase and NTPase activities of NS3 localized to amino acids 160 to 180 (dengue type 2 virus)	Li H, et al. (1999) J Virol 73:3108-3116

Genus Members

Species	Abbr.	Wild-type isolates	Host range	Membership status	Virus Code
Yellow fever virus	YFV	Asibi, French viscerotropic	mosquitoes, ticks, humans, monkeys	type species	00.026.0.01.053
Apoi virus	APOV		rodents	approved member	00.026.0.01.002
Aroa virus	AROAV	Bussuquara, Iguape, Naranjal	mosquitoes, rodents	approved member	00.026.0.01.003
Bagaza virus	BAGV	DakArb209	mosquitoes, mammals	approved member	00.026.0.01.004
Banji virus	BANV	SAH336	mosquitoes, rodents	approved member	00.026.0.01.005

Species	Abbr.	Wild-type isolates	Host range	Membership status	Virus Code
Bouboui virus	BOUV	DakArb409	mosquitoes, mammals	approved member	00.026.0.01.007
Bukalasa bat virus	BBV	UgBP111	bats	approved member	00.026.0.01.008
Cacipacore virus	CPCV	BeAn327600	birds	approved member	00.026.0.01.009
Carey Island virus	CIV	P70-1215	bats	approved member	00.026.0.01.010
Cowbone Ridge virus	CRV	W-10956	rodents	approved member	00.026.0.01.011
Dakar bat virus	DBV	Dak249	bats, humans	approved member	00.026.0.01.012
Dengue virus	DENV	DENV-1, DENV-2, DENV-3, DENV-4	mosquitoes, humans, monkeys	approved member	00.026.0.01.013
Edge Hill virus	EHV	C281	mosquitoes, marsupials, humans (rare)	approved member	00.026.0.01.014
Entebbe bat virus	ENTV	Sokuluk, IL-30	bats	approved member	00.026.0.01.015
Gadgets Gully virus	GGYV	CSIRO-122	ticks, birds, mammals	approved member	00.026.0.01.016
Ilheus virus	ILHV	Rocio	mosquitoes, birds, mammals	approved member	00.026.0.01.017
Israel turkey meningoencephalo myelitis virus	ITV		mosquitoes, birds	approved member	00.026.0.01.018
Japanese encephalitis virus	JEV	Nakayama, Beijing, JaOArS982	mosquitoes, birds, pigs, humans	approved member	00.026.0.01.019
Jugra virus	JUGV	P9-314	mosquitoes, bats (possibly)	approved member	00.026.0.01.020
Jutiapa virus	JUTV	JG-1281	rodents	approved member	00.026.0.01.021
Kadam virus	KADV	AMP6640	ticks, mammals	approved member	00.026.0.01.022
Kedougou virus	KEDV	DakAar D1470	mosquitoes, humans	approved member	00.026.0.01.023
Kokobera virus	KOKV	MRM32, Stratford (C338)	mosquitoes, marsupials, humans (rare)	approved member	00.026.0.01.024
Koutango virus	KOUV	DakAnd5443	ticks, rodents	approved member	00.026.0.01.025
Kyasanur Forest disease virus	KFDV	W371, IP9605	ticks, birds, mammals	approved member	00.026.0.01.026

Species	Abbr.	Wild-type isolates	Host range	Membership status	Virus Code
Langat virus	LGTV	TP21	ticks, rodents	approved member	00.026.0.01.027
Louping ill virus	LIV	Irish, British, Spanish, Turkish subtypes	ticks, birds, mammals	approved member	00.026.0.01.028
Meaban virus	MEAV	Brest/Ar/T-707	ticks, seabirds	approved member	00.026.0.01.029
Modoc virus	MODV	M544	rodents	approved member	00.026.0.01.030
Montana myotis leukoencephalitis virus	MMLV	USA-B-310, A564	bats	approved member	00.026.0.01.031
Murray Valley encephalitis virus	MVEV	1/51, MRM66, Alfuy, MRM3929	mosquitoes, birds, mammals	approved member	00.026.0.01.032
Ntaya virus	NTAV		mosquitoes, birds, mammals	approved member	00.026.0.01.033
Omsk hemorrhagic fever virus	OHFV	157, Kubrin, Bogolukoba, Gubriev	ticks, mammals	approved member	00.026.0.01.034
Phnom Phenh bat virus	PPBV	A38/69, Batu Cave virus	bats	approved member	00.026.0.01.035
Powassan virus	POWV	LB, Byers	ticks, mammals	approved member	00.026.0.01.036
Rio Bravo virus	RBV	M64	bats	approved member	00.026.0.01.037
Royal Farm virus	RFV	Art371, Karshi	ticks, birds, mammals	approved member	00.026.0.01.038
Saboya virus	SABV	DakAnD4600, Potiskum	sandfly, mammals	approved member	00.026.0.01.039
Sal Vieja virus	SVV	78TWM-106	rodents	approved member	00.026.0.01.040
San Perlita virus	SPV	71V1251	rodents	approved member	00.026.0.01.041
Saumarez Reef virus	SREV	CSIRO-4	ticks, seabirds	approved member	00.026.0.01.042
Sepik virus	SEPV	MK7148	mosquitoes, humans (rare)	approved member	00.026.0.01.043
St Louis encephalitis virus	SLEV	Hubbard, MSI.7, Parton	mosquitoes, ticks, birds, mammals	approved member	00.026.0.01.044
Tembusu virus	TMUV	MM1775	mosquitoes, birds, mammals	approved member	00.026.0.01.045

Species	Abbr.	Wild-type isolates	Host range	Membership status	Virus Code
Tick-borne encephalitis virus	TBEV	European, Far Eastern, Siberian subtypes	ticks, birds, mammals	approved member	00.026.0.01.046
Tyulenyi virus	TYUV	LEIV6C	ticks, seabirds, mammals	approved member	00.026.0.01.047
Uganda S virus	UGSV		mosquitoes, birds, mammals	approved member	00.026.0.01.048
Usutu virus	USUV	SAAr1776	mosquitoes, birds, humans	approved member	00.026.0.01.049
Wesselsbron virus	WESSV	van Tonder, SAH177	mosquitoes, ticks, mammals	approved member	00.026.0.01.050
West Nile virus	WNV	Nigeria (Wengler), NY, Egypt, Sarafend, Kunjin, MRM61C, MRM16	mosquitoes, ticks, birds, mammals	approved member	00.026.0.01.051
Yaounde virus	YAOV	DakArY276	mosquitoes, birds, mammals	approved member	00.026.0.01.052
Yokose virus	YOKV		mammals	approved member	00.026.0.01.054
Zika virus	ZIKV	MR766, Spondweni	mosquitoes, monkeys, humans	approved member	00.026.0.01.055
Cell fusing agent virus	CFAV		mosquitoes	tentative member	00.026.0.81.057
Tamana bat virus	TABV		mosquitoes, bats	tentative member	00.026.0.81.056

Nucleotide Sequences

Genomic region	Virus species	Strain	Nucleotides	Accession number	Reference
complete genome	Dengue virus type 1	Singapore S275/90	10717	M87512	Fu J, et al. (1992) Virology 188:953-958
complete genome	Dengue virus type 2	Jamaica	10723	M20558	Deubel V, et al. (1988) Virology 165:234-244
complete genome	Dengue virus type 3	H87	10664	M93130	Osatomi K, Sumiyoshi H (1990) Virology 176:643-647
5' untranslated sequence and structural genes	Dengue virus type 4	Caribbean 814669	2429	M14931	Zhao B, et al. (1986) Virology 155:77-88

Genomic region	Virus species	Strain	Nucleotides	Accession number	Reference
non-structural genes and 3' untranslated sequence	Dengue virus type 4	Caribbean 814669	8215	M17255	Mackow E, et al. (1987) Virology 159:217-218
complete genome	Japanese encephalitis virus	JaORS982	10976	M18370	Sumiyoshi H, et al. (1987) Virology 161:497-510
5' and 3' untranslated sequences	Kunjin virus	MRM61C	724	L24511	Khromykh AA, Westaway EG (1994) Virology 68:4580-4588
complete coding sequence	Kunjin virus	MRM61C	10664	D00246	Coia G, et al. (1988) J Gen Virol 69:1-21
structural genes	Langat virus	TP21	2328	M73835	Mandl CW (1991) Virology 185:891-895
non-structural genes	Langat virus	TP21	7917	S35365	Iacono-Connors LC, Schmaljohn CS (1992) Virology 188:875-880
complete genome	louping ill virus	369/T2	10871	Y07863	Gritsun TS, et al. (1997) Virus Research 49:27-39
5' untranslated sequence and C to NS3 genes	Murray Valley encephalitis virus	1-51	5436	X03467	Dalgarno L, et al. (1986) J Mol Biol 187:309-323
NS3 to NS5 genes and 3' untranslated sequence	Murray Valley encephalitis virus	1-51	5525		Lee E, et al. (1990) Virus Genes 4:197-213
complete genome	Murray Valley encephalitis virus	1-51	11104	AF161266	Hurrelbrink RJ, et al. (1999) J Gen Virol 80:3115-3125
complete genome	Powassan virus	LB	10838	L06436	Mandl CW (1993) Virology 194:173-184
complete genome	Tick-borne encephalitis virus	Neudoerfl	11141	M27157	Mandl CW (1995) (direct submission)
complete genome	West Nile virus	Wengler	10960	M12294	Castle E (1986) Virology 149:10-26 (and unpublished)
complete genome	Yellow fever virus	French viscerotropic	10862	U21056	Wang E, et al. (1995) J Gen Virol 76:2749-2755
complete genome	Cell fusing agent virus		10695	M91671	Cammisa-Parks H, et al. (1992) Virology 189:511-524
C to NS2B genes	St. Louis encephalitis virus	MSL.7	4673	M16614	Trent DW, et al. (1987) Virology 156:293-304

Genomic region	Virus species	Strain	Nucleotides	Accession number	Reference
complete genome	Yellow fever virus	17D (vaccine)	10862	NC002031	Rice CM, et al. (1985) Science 229:726-733

Flavivirus genome organization. In the polyprotein, upper arrows indicate cleavage sites in the cytosol by the viral serine protease NS3 and cofactor NS2B, and lower arrows cleavages in the lumen of the endoplasmic reticulum; signal sequences are shown as shaded bars. Figure prepared from data in Coia G, et al. (1988) *J Gen Virol* 69:1-21; Speight G, Westaway EG (1989) *J Gen Virol* 70:2209-2214.

Proteins

Protein	Abbr.	MW [kDa]	Time of expression	Accession Numbers	Additional information
capsid or core	C	13.5	continuous	M87512, M20588, M93130, M14931, M17255, M18370, L24511, D00246, M73835, S35365, Y07863, X03467, AF161266, L06436, M27157, M12294, X03700, M91671, M16614, U21056	binds to virion RNA in core; basic, poorly conserved; nuclear localization signal near C-terminus
precursor to M protein	prM	21-23	continuous	M87512, M20588, M93130, M14931, M18370, D00246, M73835, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	transmembrane glycoprotein; in envelope of immature virions
minor envelope protein	M	8.2-8.5	continuous	M87512, M20558, M93130, M14931, M18370, D00246, M73835, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	cleaved from prM by furin during maturation of virion

Protein	Abbr.	MW [kDa]	Time of expression	Accession Numbers	Additional information
major envelope protein	E	54-59	continuous	M87512, M20558, M93130, M14931, M18370, D00246, M73835, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	glycosylated; as dimers in virion; crystal structure known
non-structural glycoprotein	NS1	45-47	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	forms dimers, secreted as hexamers; in replicase complex
non-structural protein 2A	NS 2A	24-25	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	hydrophobic; in replicase complex
cofactor of viral protease NS3	NS2B	14.5	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	hydrophobic; conserved C-terminal octapeptide
serine protease/helicase	NS3	69-70	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, AF16126, L06436, M27157, M12294, X03700, M91671, M16614, U21056	N- terminal protease; C-terminal helicase, NTPase; in replicase complex
non-structural protein 4A	NS4A	16	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, AF16126, L06436, M27157, M12294, X03700, M91671, M16614, U21056	hydrophobic; membrane anchor role in replicase complex?

Protein	Abbr.	MW [kDa]	Time of expression	Accession Numbers	Additional information
non-structural protein 4B	NS4B	26.0-27.5	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, AF161266, L06436, M27157, M12294, X03700, M91671, M16614, U21056	hydrophobic; some nuclear localization (KUNV)
RNA-dependent RNA polymerase	NS5	104	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, AF161266, L06436, M27157, M12294, X03700, M91671, M16614, U21056	C-terminal RdRp, N-terminal methyltransferase; variable phosphorylation

Biology

Virus species	Permissive cell lines	Tissue tropism	Cytopathic effects	Additional information
Aroa virus	Vero, LLC-MK2	blood, brain	cell necrosis, plaques	CPE 6-9 days
Dengue virus types 1, 2, 3, and 4	BHK21, Vero, LLC-MK2, PS, BSC1, C6/36	blood, mononuclear phagocytes	cell necrosis, plaques, apoptosis (variable)	Dengue virus group; CPE 3-8 days (PS cells)
Japanese encephalitis virus	BHK, Vero, LLC-MK2, PS, mosquito	blood, brain, kidney, and others	cell necrosis, plaques	JEV group; mosquito-pig cycle; CPE 3-4 days
Alfuy virus	Vero, LLC-MK2, PS	blood	cell necrosis, plaques	JEV group; CPE 7-9 days
Kunjin virus	BHK21, Vero, LLC-MK2, PS, mosquito	blood	cell necrosis, plaques	JEV group; CPE 2-4 days
Murray Valley encephalitis virus	BHK21, Vero, LLC-MK2, PS, mosquito	blood, brain, spinal cord, skeletal muscle	cell necrosis, plaques	JEV group; CPE 2-5 days
St Louis encephalitis virus	BHK21, Vero, LLC-MK2, PS, mosquito	blood, brain, CNS, liver, spleen, kidney	cell necrosis, plaques	JEV group; CPE 2-4 days
West Nile virus	BHK, Vero, LLC-MK2, PS	blood, spleen, liver, lymph nodes, brain (rare)	cell necrosis, plaques	JEV group; CPE 2-4 days

Virus species	Permissive cell lines	Tissue tropism	Cytopathic effects	Additional information
Kokobera virus	BHK21, Vero, LLC-MK2, PS, HeLa	blood	cell necrosis or plaques	KOKV group; CPE 3-8 days
Stratford virus	BHK21, Vero, LLC-MK2, PS	blood	plaques (PS, LLC-MK2 cells)	KOKV group; CPE 4-8 days
Ntaya virus	BHK21, LLC-MK2	blood	cell necrosis, plaques (LLC-MK2 cells)	NTAV group; CPE 4 days
Ilheus virus	BHK21, Vero, LLC-MK2, PS	blood	cell necrosis, plaques	NTAV group; CPE 3-5 days
Rocio virus	BHK, Vero, PS	blood, brain, CNS	cell necrosis, plaques	NTAV group; CPE 2-4 days
Israel turkey meningo-encephalomyelitis virus	Vero, LLC-MK2, PS	blood, brain, CNS, liver, spleen	cell necrosis, plaques	NTAV group; CPE 3-5 days
Zika virus	LLC-MK2	blood	plaques (also in primary CEF, DEF)	Spondweni virus group; CPE 4 days
Yellow fever virus	BHK21, Vero, PS, mosquito	blood, liver, kidney	cell necrosis, plaques	YFV group; CPE about 7 days
Banzi virus	BHK21, LLC-MK2, PS	blood, liver	cell necrosis, plaques	YFV group; CPE 3-6 days
Edge Hill virus	BHK21, Vero, LLC-MK2, PS, mosquito	blood	cell necrosis, plaques	YFV group; CPE 3-15 days
Wesselsbron virus	BHK21, Vero, LLC-MK2, PS	blood, spinal cord	cell necrosis, plaques	YFV group; CPE 3-6 days
Kyasanur Forest disease virus	hamster, MK, HeLa, tick	blood, liver, kidney, spleen	cell necrosis, plaques	mammalian tick-borne group; CPE variable
Langat virus	Vero, LLC-MK2	blood, liver, kidney, spleen	cell necrosis, plaques	mammalian tick-borne group; CPE 4-9 days
Omsk haemorrhagic fever virus	BHK21, HeLa, PS	blood, CSF, kidney, spleen	cell necrosis, plaques (PS cells)	mammalian tick-borne group; CPE 2-5 days
Powassan virus	MK	blood, brain	cell necrosis, plaques	mammalian tick-borne group; CPE 5-15 days
Tick-borne encephalitis virus	Vero, HeLa, Hep2, Detroit 6	blood, brain, spinal cord	variable	mammalian tick-borne group; CPE about 6 days
Louping ill virus	Vero, LLC-MK2, PS, HeLa, Detroit 6	blood, CSF, CNS, spleen, skeletal muscles	cell necrosis, plaques	mammalian tick-borne group; CPE 4-15 days
Saumarez Reef virus	BHK21, PS	blood	cell necrosis, plaques (PS cells)	sea-bird tick-borne group; CPE 3-7 days

Virus species	Permissive cell lines	Tissue tropism	Cytopathic effects	Additional information
Entebbe bat virus	BHK21, Vero, LLC-MK2	brain, salivary gland	plaques (LLC-MK2, Vero cells)	ENTV group; no known vector; CPE 4-16 days
Modoc virus	LLC-MK2, Vero	blood, heart, liver	cell necrosis, plaques	MODV group; no known vector; CPE 2-4 days
Rio Bravo virus	LLC-MK2, Vero	blood, salivary gland	plaques	RBV group; no known vector; CPE 2-7 days
Dakar bat virus	BHK21, Vero, LLC-MK2, PS	blood, salivary gland	plaques	RBV group; no known vector; CPE 2-7 days

Diseases

Disease	Causative agent	Affected organism	characteristics	Route of transmission	Geographic distribution
dengue fever	Dengue virus types 1, 2, 3, and 4	man; monkeys if zoonotic	2 to 7 days incubation; febrile headache, joint pain, rash	Aedes mosquitoes	tropical and temperate
dengue haemorrhagic fever/shock	Dengue virus secondary infections, 3% of primary	man when sensitized	capillary leakage, haemorrhage, shock; 1 to 10% deaths	Aedes mosquitoes	tropical and temperate
Ilheus fever	Ilheus virus	man	mild, febrile headache, myalgia	mosquitoes	Brazil, Central America
Japanese encephalitis	Japanese encephalitis virus	man, pigs, birds	usually mild, febrile headache; if severe approx. 20% fatal	mosquitoes	Asia, New Guinea
Kyasanur Forest disease	Kyasanur Forest disease virus	man, small mammals, monkeys	acute, febrile headache, myalgia, haemorrhage; 4% deaths	ticks	Mysore State in India
Kunjin disease	Kunjin virus	man, birds	mild febrile illness; mild encephalitis (very rare)	mosquitoes	Australia, New Guinea
loup ing ill	Louping ill virus	mainly sheep, rarely man	neurotropic in sheep	ticks; occupat. in man	British Isles
Murray Valley encephalitis	Murray Valley encephalitis virus	man, birds	fever, headache, myalgia, coma, paralysis; 20% deaths	mosquitoes	Australia, New Guinea
Omsk haemorrhagic fever	Omsk haemorrhagic fever virus	man, rodents, birds	diphasic fever, haemorrhagic mucous membranes; 2% deaths	ticks	Siberia
Powassan disease	Powassan virus	wild mammals, rarely man	fever, encephalitis; neurological sequelae in 35% of cases	ticks	Canada, USA, Russia
Rocio encephalitis	Rocio virus	man; unknown animal host	acute, febrile headache, encephalitis; 4% deaths	mosquitoes	Brazil

Disease	Causative agent	Affected organism	characteristics	Route of transmission	Geographic distribution
St. Louis encephalitis	St. Louis encephalitis virus	man, birds	febrile headache, myalgia, meningo-encephalitis; 7% deaths	culicine mosquitoes	mainly North America
tick-borne encephalitis	Tick-borne encephalitis virus	man, rodents, insectivores	febrile headache, drowsiness, encephalitis; to 20% deaths	ticks; cow/goat's milk	Europe and Russia
Wesselsbron disease	Wesselsbron virus	sheep, goats, cows	fever, myalgia, rash; abortion in ewes; lethal in goats	mosquitoes	Africa and Thailand
West Nile fever	West Nile virus	man, birds	usually mild, fever and rash, rarely encephalitis	mosquitoes, ticks	Eurasia, Africa, New York
yellow fever (urban and jungle)	Yellow fever virus	man, monkeys	febrile headache, myalgia, vomiting, jaundice; 30% deaths	Aedes mosquitoes	tropical Africa, America
Zika disease	Zika virus	man, monkeys	rare in man, fever, headache, rash	mosquitoes	Central Africa, Indonesia

Vaccine Strains

Strain	Attenuation procedure	Additional information	Reference
Yellow fever virus 17D (attenuated Asibi strain)	many serial passages in chick embryo	68 point mutations compared to wild type virus	Theiler M, Smith HH (1939) J Exp Med 65:787-800
Japanese encephalitis virus strain Nakayama	formalin inactivated tissue extract	BIKEN vaccine, purified from infected mouse brain	Poland JD, et al. (1990) J Infect Dis 161:878-882
Japanese encephalitis virus strain SA14-14-2	serial passages in primary hamster kidney cells	vaccine produced in primary hamster kidney cells	Liu Z-L, et al. (1997) J Infect Dis 176:1366-1369
Tick-borne encephalitis virus Western subtype	formalin inactivation	purified vaccine grown in chick embryos	Kunz C, et al. (1980) J Med Virol 6:103-109
Louping ill virus	formalin inactivation	for sheep; grown in sheep kidney cell cultures	Brotherstone JG, Boyce JB (1970) J Comp Pathol 80:377-388

Vector Constructs

Vector	Backbone strain	Application	Insertion capacity [kb]	Additional information	Reference
Kunjin replicon RNA	Kunjin virus strain MRM61C	expression	>3	non-cytopathic self-replicating subgenomic RNA	Khromykh AA, Westaway EG (1997) J Virol 71:1497-1505

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- [9] Rothman AL, Ennis FA (1999) Immunopathogenesis of dengue haemorrhagic fever. *Virology* 257:1-6
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Hepacivirus

Flaviviridae

GIOVANNA BARBA SPAETH and CHARLES M. RICE

Virion

Morphology spherical
 Envelope yes
 Diameter [nm] 55-65
 Length [nm] n/a
 Structural components. . . nucleocapsid (RNA+capsid protein), bilayer, glycoproteins
 Buoyant density [g/mL] . . 1.07-1.22
 Additional information. . . low density lipoprotein-associated; higher density cores or Ab-associated

Genome

Nucleic acid RNA
 Strandedness single-stranded
 Polarity positive-sense
 Configuration linear
 Segments. 1
 Size [kb]. 9.6
 G+C content [%]. 54-59
 Transcription units 1
 Additional information. . . 5' NCR contains a IRES element, translation of mRNA is CAP-independent

Replication Strategy

Entry mechanism receptor-mediated endocytosis? CD81? LDLR?
 Site of transcription. . . . n/a
 Transcriptase n/a
 Site of genome replication cytoplasm in association with cellular membranes
 Replicase virus-encoded RNA-dependent RNA polymerase, host factors?
 Replication intermediate . negative strand RNA
 Site of virion assembly . . budding into intracytoplasmic vesicles
 Egress mechanism exocytosis?
 Additional information. . . hepatotropic

History

Year	Event	Reference
1975	Identification of a nonA-nonB hepatitis (NANBH) agent as the major cause of transfusion-associated hepatitis	Feinstone SM, et al. (1975) N Engl J Med 292:767-770
1978	Chimpanzees as an animal model for NANBH	Tabor R, et al. (1978) Lancet 1:463-466; Hollinger FB, et al. (1978) Intervirology 10:60-68
1986-1989	Treatment with interferon α	Hoofnagle JH, et al. (1986) N Engl J Med 315:1575-1578; Davis GL, et al. (1989) N Engl J Med 321:1501-1506; Di Bisceglie AM, et al. (1989) N Engl J Med 321:1506-1510
1989	Molecular cloning of the NANBH agent; designation as hepatitis C virus (HCV)	Choo Q-L, et al. (1989) Science 244:359-362
1990	Association with hepatocellular carcinoma	Saito I, et al. (1990) Proc Natl Acad Sci USA 87:6547-6549
1992	Absence of protective immunity	Prince AM, et al. (1992) J Hepatol 16:219-223; Farci P, et al. (1992) Science 258:135-140
1992-1993	E2 hypervariable region and immune selection	Weiner AJ, et al. (1992) Proc Natl Acad Sci USA 89:3468-3472; Kato N, et al. (1993) J Virol 67:3923-30
1992	The 5' non-coding region functions as an IRES element	Tsukiyama-Kohara K, et al. (1992) J Virol 66:1476-1483
1993	Association of HCV particles with lipoproteins and immunoglobulins	Thomssen R, et al. (1993) Med Microbiol Immunol 182:329-334; Hijikata M, et al. (1993) J Virol 67:1953-1958
1993	Identification of HCV polyprotein cleavage products	Grakoui, et al. (1993) J Virol 67:1385-1395; Hijikata M, et al. (1993) Proc Natl Acad Sci USA 90:10773-10777
1993	Characterization of HCV NS3 serine protease	Grakoui A, et al. (1993) J Virol 67:2832-2843; Tomei L, et al. (1993) J Virol 67:4017-4026; Hijikata M, et al. (1993) J Virol 67:4665-4675
1993	Discovery of a second HCV protease: HCV NS2-3 autoprotease	Grakoui A, et al. (1993) Proc Natl Acad Sci USA 90:10583-19587; Hijikata M, et al. (1993) J Virol 67:4665-4675
1994	Characterization of HCV core protein	Santolini E, et al. (1994) J Virol 68:3631-3641
1994	Characterization of HCV envelope proteins	Dubuisson J, et al. (1994) J Virol 68:6147-6160; Lin C, et al. (1994) J Virol 68:5063-5073
1995	Analysis of HCV-specific CTL response and cytokine release	Koziel MJ, et al. (1995) J Clin Invest 96:2311-2321; Battegay M, et al. (1995) J Virol 69:2462-2470
1995-1999	Interferon-sensitivity determining region (ISDR) in NS5A?	Enomoto N, et al. (1995) J Clin Invest 96:224-230; Nakano I, et al. (1999) J Hepatol 30:1014-1022

Year	Event	Reference
1995	Molecular cloning of GBV-A and GBV-B	Simmons P, et al. (1995) Proc Natl Acad Sci USA 92:3401-3405; Muerhoff AS, et al. (1995) J Virol 69:5621-5630
1995-1996	Characterization of HCV 3' non-coding region	Tanaka T, et al. (1995) Biochem Biophys Res Commun 215:744-749; Kolykhalov AA, et al. (1996) J Virol 70:3363-3371
1995	Treatment with interferon and ribavirin	Reichard O, et al. (1997) Hepatology 26:108S-111S
1996	Crystal structure of HCV NS3 protease	Love RA, et al. (1996) Cell 87:331-342; Kim JL, et al. (1996) Cell 87:343-355
1996-1999	Characterization of HCV NS5B RNA-dependent RNA polymerase/Crystal structure of HCV NS5B polymerase	Behrens S, et al. (1996) EMBO J 15:12-22; Lohmann V, et al. (1997) J Virol 71:8416-8428; Lesburg CA, et al. (1999) Nat Struct Biol 6:937-943
1997-1998	Interference of HCV core protein with cellular signal transduction pathways	Matsumoto M, et al. (1997) J Virol 71:1301-1309; Chen CM, et al. (1997) J Virol 71:9417-9426; Zhu N, et al. (1998) J Virol 72:3691-3697
1997	Correlation between HCV core expression and steatosis	Barba G, et al. (1997) Proc Natl Acad Sci USA 94:1200-1205
1997-1999	Successful engineering HCV infectious cDNAs clones	Kolykhalov AA, et al. (1997) Science 277:570-574; Yanagi M, et al. (1997) Proc Natl Acad Sci USA 94:8738-8743; Yanagi M, et al. (1999) Virology 262:250-263
1997-1998	Repression of interferon induced PKR by HCV NS5A	Gale MJ, et al. (1997) Virology 230:217-227; Gale MJ, et al. (1998) Mol Cell Biol 18:5208-5218
1997-1998	Crystal structure of HCV NS3 helicase	Yao N, et al. (1997) Nat Struct Biol 4:463-467; Kim JL, et al. (1998) Structure 6:89-100
1998-1999	CD81 as a possible HCV receptor	Pileri P, et al. (1998) Science 282:938-941; Rice CM (1999) Hepatology 29:990-992
1998	Induction of HCC in HCV core transgenic mice	Moriya K, et al. (1998) Nat Med 4:1065-1067
1999-2000	Immune correlates of resolution versus chronic infection	Cooper S, et al. (1999) Immunity 10:439-449; Takaki A, et al. (2000) Nat Med 6:578-582; Lechner F, et al. (2000) J Exp Med 191:1499-1512
1999-2000	Replication of subgenomic HCV RNAs in cell culture	Lohmann V, et al. (1999) Science 285:110-113; Blight KJ, et al. (2000) Science 290:1972-1974

Genus Members

Species	Abbr.	Synonym	Wild-type isolates	Host range	Membership status	Virus Code
Hepatitis C virus	HCV		1, H, J	humans, chimpanzee	type species	00.026.0.03.001

Species	Abbr.	Synonym	Wild-type isolates	Host range	Membership status	Virus Code
GB virus B	GBV-B		HGU22304	tamarins, human origin?	tentative member	00.026.0.05.001

Nucleotide Sequences

Genomic region	Virus species	Strain	Nucleotides	Accession number	Reference
genomic RNA	HCV-1	1a, Clade 1	9379	M62321	Choo Q-L, et al. (1991) Proc Natl Acad Sci USA USA 88:2451-2455
genomic RNA	HCV-J	1b, Clade 1	9413	D90208	Kato N, et al. (1990) Jpn J Cancer Res 81:1092-1094
genomic RNA	HC-G9	1c, Clade 1	9487	D14853	Okamoto H, et al. (1994) J Gen Virol 75:629-635
genomic RNA	HC-J6	2a, Clade 2	9589	D00944	Okamoto H, et al. (1994) J Gen Virol 75:629-635
genomic RNA	HC-J8	2b, Clade 2	9511	D10988	Okamoto H, et al. (1992) Virology 188:331-341
genomic RNA	BEBE1	2c , Clade 2	9513	D50409	Nakao H, et al. (1996) Arch Virol 141:701-704
genomic RNA	NZL1	3a, Clade 3	9456	D17763	Sakamoto M, et al. (1994) J Gen Virol 75:1761-1768
genomic RNA	HCV-Tr	3b, Clade 3	9444	D49374	Chayama K, et al. (1994) J Gen Virol 75:3623-3628
genomic RNA	JK049	(10a), Clade 3	9450	D63821	Tokita H, et al. (1996) J Gen Virol 77:293-301
genomic RNA	ED43	4a, Clade 4	9355	Y11604	Chamberlain R, et al (1997) J Gen Virol 78:1341-1347
genomic RNA	EUH1480	5a, Clade 5	9343	Y13184	Cahmberlain R, et al. (1997) Biochem Biophys Res Commun 236:44-49
genomic RNA	EUHK2	6a, Clade 6	9340	Y12083	Adams NJ, et al. (1997) Biochem Biophys Res Commun 234:393-396
genomic RNA	JK046	(11a), Clade 6	9461	D63822	Tokita H, et al. (1996) J Gen Virol 77:293-301
genomic RNA	GBV-B		9143	HGU22304	Simons JN, et al. (1995) Proc Natl Acad Sci USA USA 92:3401-3405

Genome organization of Hepatitis C virus. Shown are the features of the HCV genome RNA, the polyprotein processing enzymes and sites, and the properties of the resulting HCV proteins.

Proteins

Protein	Abbr.	MW [kDa]	Additional information
capsid or core protein	C	19-22	perinuclear, multiple effects on host
envelope protein 1	E1	31	N glycans, E1E2 heterodimers, ER retention
envelope protein 2	E2	70	N glycans, E1E2 heterodimers, ER retention, HVR1
p7	p7	7	hydrophobic, partial cleavage from E2 (E2-p7)
non-structural protein 2	NS2	21	Zn-stimulated NS2-3 autoprotease
non-structural protein 3	NS3	70	serine protease, NTPase, helicase
non-structural protein 4A	NS4A	6	membrane association, NS3 serine protease cofactor
non-structural protein 4B	NS4B	27	unknown function, replicase component
non-structural protein 5A	NS5A	56-58	serine phosphoprotein, PKR inhibitor
non-structural protein 5B	NS5B	68	RNA-dependent RNA polymerase
core protein	GBV-B C		
envelope E1	GBV-B E1		
envelope E2	GBV-B E2		
putative NS2/NS3 zinc-dependent thiol protease	GBV-B NS2/NS3		

Protein	Abbr.	MW [kDa]	Additional information
putative chymotrypsin-like protease/RNA helicase	GBV-B NS3		
non-structural protein 4A	GBV-B NS4A		
non-structural protein 4B	GBV-B NS4B		
non-structural protein 5A	GBV-B NS5A		
putative RNA-dependent RNA polymerase	GBV-B NS5B		putative RNA-dependent RNA polymerase

Biology

Virus species	Permissive cell lines	Tissue tropism	Cytopathic effects	Additional information
HCV	hepatocytes, lymphocytes, other cells?	liver	unknown	difficult to propagate in cell culture
GBV-B	none reported	liver	unknown	origin unknown (tamarins?); replicates in tamarins

Diseases

Disease	Causative agent	Affected organism	characteristics	Route of transmission	Geographic distribution
acute hepatitis	HCV (immune-mediated?)	human	elevated ALT (onset 8-12 weeks), jaundice	blood	world-wide
chronic hepatitis	HCV (immune-mediated?)	human	elevated ALT, inflammation, necrosis, steatosis		world-wide
chronic active hepatitis	HCV (immune-mediated?)	human	necroinflammation		world-wide
cirrhosis	HCV (immune-mediated?)	human	necroinflammation, fibrosis, liver failure		world-wide
hepatocellular carcinoma (HCC)	HCV (liver damage?)	human	typical onset 20-30 years; associated with cirrhosis		world-wide
mixed cryoglobulinemia (MC)	HCV (Ag/Ab complexes?)	human	cryoprecipitable circulating immune complexes, arthralgia		world-wide
porphyria cutanea tarda	HCV (genetic factors?)	human	photosensitivity, hyperpigmentation, sclerodermoid plaques		world-wide
B-cell non-Hodgkin's lymphoma	HCV (lymphotropism?)	human	fever, lymphoproliferative disease		world-wide

Key References

- [1] Alter MJ (1997) *Hepatology* 26:62-65
- [2] Brechot C (1998) *Hepatogastroenterology* 45:1189-1196
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- [8] <http://www.medscape.com/23593.rhtml>
- [9] http://odp.od.nih.gov/consensus/cons/105/105_statement.htm
- [10] <http://s2as02.genes.nig.ac.jp>

Pestivirus
Flaviviridae

PAUL BECHER and HEINZ-JÜRGEN THIEL

Pestivirus of giraffe. Ultrathin section of extracellular mature virions. Length of bar [nm]: 100 [with permission of M. König, Institut für Virologie, 35392 Giessen, Germany]

Virion

- Morphology spherical
- Envelope yes
- Diameter [nm] 40-60
- Length [nm] n/a
- Structural components. . . capsid protein (C), glycoproteins (E-rns, E1, E2)
- Buoyant density [g/mL] . . 1.10-1.15
- Additional information. . . the virion envelope has 10-12 nm ring-like subunits on its surface

Genome

- Nucleic acid RNA
- Strandedness single-stranded
- Polarity positive-sense
- Configuration linear
- Segments. 1
- Size [kb]. 12.3
- G+C content [%]. 45-48
- Transcription units 1
- Additional information. . . one large open reading frame flanked by nontranslated regions (NTR); 5' end without cap; 5' region contains IRES; 3' end without poly(A)

Replication Strategy

- Entry mechanism probably receptor-mediated endocytosis
- Site of transcription. cytoplasm
- Transcriptase RNA-dependent RNA polymerase (NS5B)
- Site of genome replication . cytoplasm
- Replicase RNA-dependent RNA polymerase and additional non-structural proteins
- Replication intermediate . double-stranded RNA
- Site of virion assembly . . . intracellular membranes
- Egress mechanism exocytosis
- Additional information. . . translation initiation occurs by a cap-independent mechanism by use of an internal ribosome entry site (IRES) within the 5' region

History

Year	Event	Reference
1903	Identification of CSFV as causative agent of an infectious disease in pigs first described in 1833	DeSchweinitz EA, Dorset M (1903) US Ann Ind Citt 41, Washington
1946	First description of BVDV as causative agent of a transmissible disease in cattle	Olafson P, et al. (1946) Cornell Vet 36:205-213
1953	First description of fatal mucosal disease in cattle	Ramsey FK, Chivers WH (1953) North Am Vet 34:629-633
1959	First description of border disease in sheep	Hughes E, et al. (1959) Vet Rec 71:313-317
1960	Demonstration of antigenic relationship between BVDV and CSFV	Darbyshire JH (1960) Vet Rec 72:331-333
1988	Determination of the complete genomic sequence and genetic organization of BVDV	Collett MS, et al. (1988) Virology 165:191-208
1996	First description of a full-length pestivirus cDNA from which infectious RNA was transcribed	Moormann RJM, et al. (1996) J Virol 70:763-770
1998	First description of a subgenomic pestivirus replicon	Behrens SE, et al. (1998) J Virol 72:2364-2372

Genus Members

Species	Abbr.	Synonym	Wild-type isolates	Host range	Membership status	Virus Code
Bovine viral diarrhea virus 1	BVDV-1		NADL, Osloss, SD-1, CP7	cattle, other ruminants, pigs	type species	00.026.0.02.003
Bovine viral diarrhea virus 2	BVDV-2		890, CD87, Giessen-1, BD-78	cattle, other ruminants, pigs	approved member	00.026.0.02.004
Border disease virus	BDV		Moredu, X818, BD-31, L83-84	sheep, pigs	approved member	00.026.0.02.002
Classical swine fever virus	CSFV	Hog cholera virus	Alfort, Brescia, Alfort-T	pigs	approved member	00.026.0.02.005
Pestivirus of giraffe			H138 (Giraffe-1)	giraffe	tentative member	00.026.0.82.006

Nucleotide Sequences

Genomic region	Virus species	Strain	Nucleotides	Accession number	Reference
complete genome	BVDV-1	NADL	12573	M31182	Collett MS, et al. (1988) Virology 165:191-199

Genomic region	Virus species	Strain	Nucleotides	Accession number	Reference
complete genome	BVDV-2	890	12513	U18059	Ridpath JF, Bolin SR (1995) Virology 212:39-46
complete genome	BDV	X818	12333	AF037405	Becher P, et al. (1998) J Virol 72:5165-5173
complete genome	CSFV	Alfort-T	12297	J04358	Meyers G, et al. (1989) Virology 171:555-567

Pestivirus genome organization. The genomic RNA is usually about 12.3 kb long and contains one open reading frame flanked by 5' and 3' nontranslated regions (NTR); the proteinases involved in polyprotein processing are indicated.

Proteins

Protein	Abbr.	MW [kDa]	Accession Numbers	Additional information
N-terminal protease	N-pro	23	M31182, U18059, AF037405, J04358	non-structural protein; autoprotease
capsid protein	C	14	M31182, U18059, AF037405, J04358	structural protein
envelope protein Erns	E-rns	44-48	M31182, U18059, AF037405, J04358	glycoprotein; homodimers; secreted; RNase activity
envelope protein E1	E1	25-33	M31182, U18059, AF037405, J04358	glycoprotein; forms E1/E2 heterodimers
envelope protein E2	E2	53-55	M31182, U18059, AF037405, J04358	glycoprotein; forms E1/E2 heterodimers, homodimers
protein p7	p7	7	M31182, U18059, AF037405, J04358	probably non-structural protein
non-structural protein NS2-3	NS2-3	120-125	M31182, U18059, AF037405, J04358	serine protease, helicase, NTPase, zinc finger

Protein	Abbr.	MW [kDa]	Accession Numbers	Additional information
non-structural protein NS2	NS2	38-54	M31182, U18059, AF037405, J04358	zinc finger; processing product of NS2-3
non-structural protein NS3	NS3	75-80	M31182, U18059, AF037405, J04358	serine protease, helicase, NTPase
non-structural protein NS4A	NS4A	7-10	M31182, U18059, AF037405, J04358	cofactor for serine protease NS3
non-structural protein NS4B	NS4B	30	M31182, U18059, AF037405, J04358	
non-structural protein NS5A	NS5A	58-70	M31182, U18059, AF037405, J04358	phosphorylated
non-structural protein NS5B	NS5B	75-78	M31182, U18059, AF037405, J04358	RNA-dependent RNA polymerase

Biology

Virus species	Permissive cell lines	Tissue tropism	Cytopathic effects	Additional information
BVDV-1	MDBK, other bovine/ovine cells	particularly lymphoreticular tissue	plaque formation and extensive cytopathology	most field isolates are non-cytopathogenic
BVDV-2	MDBK, other bovine/ovine cells	particularly lymphoreticular tissue	plaque formation and extensive cytopathology	most field isolates are non-cytopathogenic
BDV	ovine and bovine cells	particularly lymphoreticular tissue	plaque formation and extensive cytopathology	almost all field isolates are non-cytopathogenic
CSFV	PK-15, other porcine cells	particularly lymphoreticular tissue	plaque formation and extensive cytopathology	almost all field isolates are non-cytopathogenic

Diseases

Disease	Causative agent	Affected organism	characteristics	Route of transmission	Geographic distribution
bovine viral diarrhoea (BVD)	BVDV-1, BVDV-2	cattle	mild or inapparent disease; abortion, malformations	oronasal, transplacental	world-wide
mucosal disease (MD)	BVDV-1, BVDV-2	cattle	bloody diarrhea; erosions/ulcerations; fatal disease	complex pathogenesis	world-wide
hemorrhagic syndrome (HS)	BVDV-2, (BVDV-1)	cattle	hemorrhages at mucosal surfaces and inner organs	oronasal	North America, Europe

Disease	Causative agent	Affected organism	characteristics	Route of transmission	Geographic distribution
border disease (BD)	BDV, BVDV-1, BVDV-2	sheep	abortion, stillbirth; hairy fleece, tremor, ataxia	oronasal, transplacental	world-wide
classical swine fever (CSF)	CSFV	pig	high fever; hemorrhages at outer skin and inner organs	oronasal, transplacental	world-wide (not US, Aus.)

Vaccine Strains

Strain	Attenuation procedure	Additional information	Reference
BVDV-1 strain Oregon C24V	passages in bovine cells	cytopathogenic virus	Gillespie JH, et al. (1960) Cornell Vet 50:73-79
BVDV-1 strain NADL	passages in bovine cells	cytopathogenic virus	Gutekunst (1963) Can J Comp Med Vet Sci 27:121-123
BVDV-1 strain RIT 4350	chemically treated	temperature-sensitive cytopathogenic virus	Lobmann M, et al. (1984) Am J Vet Res 45:2498-2503
CSFV Chinese strain (C-strain)	several hundreds of serial passages in rabbits		Baker JA (1946) Proc Soc Ex Biol Med 63:183-185

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- [4] Meyers G, Thiel H-J (1996) Adv Vir Res 47:53-118