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# Host-Virus Specificity of the Morbillivirus Receptor, SLAM, in Marine Mammals: Risk Assessment of Infection Based on Three-Dimensional Models

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Additional information is available at the end of the chapter

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## 1. Introduction

Incidences of infectious diseases in marine mammals have been increasing [1]. Among them, morbillivirus infection is the greatest threat to marine mammals because it has caused mass die-offs in several pinniped and cetacean species in the past few decades [2,3]. The genus *Morbillivirus* belongs to the family Paramyxoviridae, and the viruses in this genus have a genome consisting of a single piece of negative-stranded RNA, which encodes eight viral proteins: a nucleocapsid protein (N); a phosphoprotein (P); two virulence factors (C and V); a matrix protein (M); a membrane fusion protein (F); a hemagglutinin binding protein (H); and an RNA polymerase (L) [4]. The two viral surface glycoproteins, H and F, play important roles during the viral infection of host cells. The H protein is required for viral attachment to the host cells, while the F protein mediates membrane fusion with the host plasma membrane and enables the entry of the virus.

Until the discovery of a new morbillivirus in marine mammals in 1988, only four morbillivirus species had been identified in land mammals: the measles virus (MV); rinderpest virus (RPV); peste des petits ruminants virus (PPRV); and canine distemper virus (CDV) [4]. The new morbillivirus was isolated from dead harbor seals (*Phoca vitulina*) in a mass die-off around the Baltic and North Sea coasts and was named phocine distemper virus (PDV) [5,6]. Two other new viruses originating in cetaceans were also isolated from dead harbor porpoises (*Phocoena phocoena*) and striped dolphins (*Stenella coeruleoalba*) and were named porpoise morbillivirus (PMV) and dolphin morbillivirus (DMV) [7,8]. Based on the similarities of the gene sequences, it was proposed that the cetacean-origin viruses be unified as a single species, cetacean morbillivirus (CMV) [9,10].

Morbilliviruses propagate primarily in lymphoid tissues and induce acute disease. They are usually accompanied by lymphopenia and immunosuppression, which often lead to secondary, opportunistic infections in the host. The distemper viruses, CDV and PDV, often invade the central nervous systems of their hosts, although acute encephalitis is not common in other morbillivirus infections [4]. A notable feature of morbilliviruses is their high host specificity. The natural host of MV is humans, but it can also infect monkeys. Ruminants are the targets of RPV and PPRV. RPV mainly infects cattle, while PPRV infects goats and sheep. Although these viruses have multiple host compatibilities, they induce more severe disease in the primary hosts than in others [11,12]. The natural host for CDV is dogs, but ferrets (*Mustela putorius furo*) have been used as an experimental model due to their high sensitivity to CDV. Recently, the host range of CDV has been shown to be wider than previously thought and expanded to include other wild carnivores, such as Baikal seals (*Phoca sibirica*) or lions (*Panthera leo*) [13-15]. PDV and CMV have been isolated only from seals and cetaceans, respectively. While no morbilliviruses have been isolated from sirenians, serologic evidence of exposure to morbillivirus was reported in manatees (*Trichechus manatus*) without showing clinical signs of disease [16,17].

The cellular receptor of a virus is one of the major determinants of host specificity and tissue tropism. The signaling lymphocyte activation molecule (SLAM) has recently been shown to be the principal cellular receptor for morbilliviruses in humans, cows, and dogs [18,19]. SLAM itself was first discovered in 1995 as a novel receptor molecule involved in T-cell activation [20]. It is expressed on various immune cells, such as thymocytes, activated T and B cells, mature dendritic cells, macrophages, and platelets [21,22]. SLAM is also a marker for the most primitive hematopoietic stem cells [23]. The distribution and function of SLAM are consistent with the cell tropism and immunosuppressive nature of morbilliviruses. This indicates that the host range of morbillivirus may be explained by key amino acid residues of SLAM on the interface with morbillivirus.

In this chapter, we review morbillivirus infection in marine mammals and its possible primary receptor in the host, SLAM. Further, we discuss host-virus specificities based on three-dimensional models of SLAM and risk assessment of morbillivirus infection in marine mammals.

## **2. Morbillivirus infection and its impact on marine mammals**

### **2.1. Mass die-offs in marine mammals and discovery of new morbilliviruses**

Since the late 1980s, many mass die-offs have been reported around the coasts of Europe and the USA (Table 1). Approximately 18,000 harbor seals and several hundred grey seals (*Halichoerus grypus*) were found dead on northern European coasts in 1988–1989. The distemper-like gross observations suggested that a morbillivirus could have been the causative agent [6]. Detailed serological, virological, and immunohistochemical examinations showed that the agent was a new member of the genus *Morbillivirus*, named phocine distemper virus (PDV) [5,24]. In 2002, PDV again killed at least 21,000 seals

inhabiting the same locales [25,26]. About the same time as the first outbreak on northern European coasts, in 1987–1988 the deaths of approximately 18,000 Baikal seals were reported in Lake Baikal which showed clinical signs identical to those reported in European seals [13]. However, subsequent genomic characterization revealed that the cause of the mass die-off of Baikal seals was CDV [27–31]. CDV also induced another mass die-off among Caspian seals (*Phoca caspica*), in which many seals died in 1997 and 2000, near Azerbaijan on the western shores of the Caspian Sea [32,33].

Date	Site	Animal species	No. of dead	Virus
1987-1988	USA Atlantic coast	<i>Tursiops truncatus</i>	>2,500	CMV
1987-1988	Lake Baikal	<i>Phoca sibirica</i>	>18,000	CDV
1988	North & Baltic Sea	<i>Phoca vitulina</i>	>18,000	PDV
1990	Mediterranean Sea	<i>Stenella coeruleoalba</i>	>2,000	CMV
1993	Mexican Gulf	<i>Tursiops truncatus</i>	>1,000	CMV
1997	Caspian Sea	<i>Phoca caspica</i>	>2,000	CDV
2000	Caspian Sea	<i>Phoca caspica</i>	>10,000	CDV
2002	North & Baltic Sea	<i>Phoca vitulina</i>	>21,000	PDV

CMV, cetacean morbillivirus; CDV, canine distemper virus; PDV, phocine distemper virus.

**Table 1.** Mass die-offs of marine mammals caused by morbilliviruses.

The first evidence of morbillivirus infection in cetaceans was described in several stranded harbor porpoises with pathological changes on the Irish coastline in 1988 [7]. A new morbillivirus was isolated and termed PMV for “porpoise” [34]. Since 1990, a severe mass die-off began to affect the striped dolphin (*Stenella coeruleoalba*) population on the Mediterranean coast of Spain and rapidly spread throughout the western Mediterranean Sea, including the coasts of France, Italy, Greece, and Turkey [8,35] (Table 1). A new virus, named DMV for “dolphin” was isolated as the causative agent [9]. A retrospective serologic investigation indicated that PMV and DMV were the agents responsible for another epidemic in bottlenose dolphins (*Tursiops truncatus*) along the Atlantic coast of the USA, for which the causative agent had been initially thought to be brevetoxin produced by a marine dinoflagellate (*Ptychodiscus brevis*) [36–38]. PMV also induced a die-off of bottlenose dolphins in the Gulf of Mexico during 1993–1994 [37–39]. Molecular biological analyses of these cetacean morbilliviruses showed that their gene sequences were similar [9,10]. Based on the similarities, it was proposed that these cetacean morbilliviruses be classified as a single species called CMV.

Thus, morbillivirus infection has a strong impact on populations of marine mammals, as listed in Table 1. In addition to mass die-offs, many smaller-scale die-offs were reported in various oceans. Even if the scale is small, outbreaks of morbillivirus infection can have serious consequences for marine mammal populations, especially among endangered species at risk of extinction, such as Mediterranean monk seals (*Monachus monachus*). In 1997, approximately 50% of the population of Mediterranean monk seals residing along the

coast of Mauritania in Africa died suddenly. Morbilliviruses were isolated from the dead seals, although distemper-like lesions were not detected in the animals [40]. Hence, it remains unclear whether morbillivirus was the agent responsible for the dramatic deaths. The involvement of an algal bloom was also suggested as the primary cause [41]. In any case, when populations of many marine mammal species are decreasing, morbillivirus infection may cause a fatal blow.

## 2.2. Transmission and maintenance reservoir of marine morbilliviruses

The origin, precise mode of transmission, and maintenance reservoir of morbilliviruses causing die-off epidemics in marine mammals remain to be elucidated. Morbilliviruses proliferate in the infected animal for a short time after infection but do not persist in the host [4]. After being shed from the infected host, they do not survive long in the environment [4]. For the transmission of morbilliviruses, therefore, close contact between acutely infected and susceptible animals is required. In addition, because a morbillivirus infection results in lifelong immunity in the infected animal, when the virus is maintained in an animal population, a constant supply of new susceptible animals is needed. It has been calculated that the minimal population size for MV maintenance is approximately 300,000 individuals [42]. In the mass die-off of European seals in 1988, the most likely viral source was an infected seal population in the Arctic region, which moved southward and made contact with the population on the European coast. This hypothesis was based on the results of serologic studies using archival seal sera. PDV-specific antibodies were not observed in European seal sera before 1988, indicating that the population was naive and had not been previously exposed to the virus [43]. However, specific antibodies were detected in sera obtained from arctic seals long before 1998 [44,45]. In addition, alterations in the migration patterns of Arctic harp seal (*Phoca groenlandica*) populations were recorded. They were seen much farther south than usual in northern European waters in the year prior to the epizootic of the harp seal population [46]. The harp seal population is extremely large, with four million individuals in Canadian waters alone, which is sufficient to maintain morbillivirus circulating within the population. Subclinically or subacutely affected animals might play an important role in the transmission of the virus.

It should be noted that morbillivirus transmission sometimes occurs between marine and land mammals. As described above, the mass die-offs of Baikal seals and Caspian seals were caused by infection with CDV [28,30,32]. The most likely source of infection was land animals infected with CDV, because outbreaks were common among the numerous feral and domestic dogs around the lake [47]. Accidental infection in the opposite direction was also reported. A farmed mink population fed infected seal meat was infected with PDV in Denmark during the 1988 epizootic of PDV [48].

## 3. SLAM, a receptor of morbillivirus

The characteristics of SLAM have been extensively studied in humans. SLAM (CD150) is a type I transmembrane protein, and there are many members of the SLAM family including

the well-known 2B4 (CD244), Ly-9 (CD229), NTB-A, and CD84 [49]. All of the SLAM family members have an extracellular region composed of a membrane-distal immunoglobulin variable (V) domain and a membrane-proximal immunoglobulin constant-2 (C2) domain, along with a cytoplasmic region bearing multiple tyrosine-based switch motifs (ITSMs) that bind cytoplasmic Src homology-2 (SH2)-containing proteins such as SLAM-associated protein (SAP) [50]. Evidence is accumulating that the interaction between the cytoplasmic region of SLAM and SAP family molecules mediates a switch to positive or negative signaling in immune cells and plays a crucial role in multiple immune regulations [22]. Genes for the SLAM family receptors are located within a ~400-kb cluster on chromosome 1 in humans and mice [51]. This gene location, coupled with the conserved exon-intron structure of SLAM-related genes, implies that they were generated by the sequential duplication of a single ancestral gene. A SLAM family receptor forms a homophilic dimer by weak binding between the V domains and acts as a self-ligand, suggesting that the receptors can trigger homotypic or heterotypic cell-cell interactions [52]. The V domain of SLAM (CD150) also provides an interface for binding with morbilliviruses [53]. The viral H protein has a strong affinity for the V domain of SLAM, which is 400-fold higher than for self-ligand interaction [54]. The interaction between the viral H protein and SLAM V domain is the initial event in infection with morbilliviruses. The results of recent detailed structural studies have suggested that the interaction changes the microenvironment of the interaction zone for the fusion activity of the F protein, although the mechanism of membrane fusion mediated by the F protein is not fully understood [55-58].

### 3.1. History of the discovery of the morbillivirus receptor

The human CD46 molecule was first identified as a cellular receptor for Edmonston vaccine strains of MV [59,60]. The Edmonston strain was isolated from the blood and throat washings of a child with measles using primary human kidney cells in 1954 [61]. It was later adapted to chick embryo fibroblasts and is being used as an attenuated vaccine [62]. This strain grows well in many cell lines, such as Vero cells, and has become the most extensively studied MV strain in the laboratory. However, because CD46, a complement-regulatory molecule, is expressed on all human nucleated cells, its ubiquitous distribution cannot explain the lymphoid tropism of MV. At present, CD46 is thought to be a specific receptor of the Edmonston strain, which is presumed to acquire the ability to use CD46 by adapting to cultured human kidney cells.

On the other hand, many wild-type strains have been isolated from clinical samples using the marmoset B cell line (B95a) [63], but they do not grow on many CD46+ cell lines. In order to identify the receptor for wild-type MV, functional expression cloning of a cDNA library of B95a cells was carried out using the VSV pseudotype system. SLAM was shown to be a cellular receptor for wild-type MV [18]. CDV and RPV were also shown to use canine and bovine SLAMs for entry into host cells [19]. Thus, SLAM is thought to be the major receptor for wild-type morbilliviruses.

Recently, Nectin 4, a cellular adhesion junction molecule, has been identified as the third receptor for MV in polarized epithelial cells [64,65]. Infection experiments in monkeys

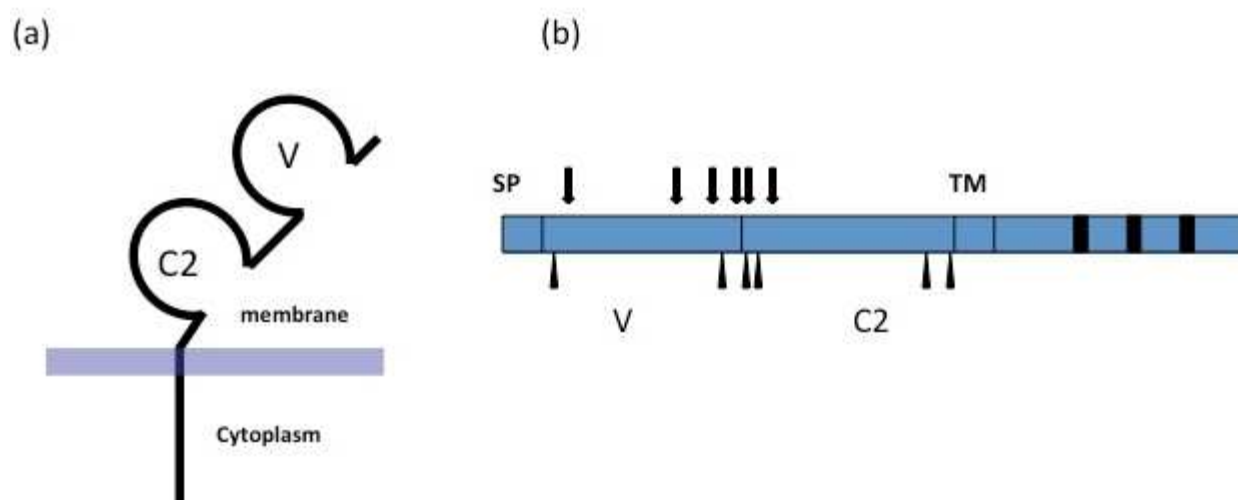
showed that MV initially targets SLAM-positive immune cells such as alveolar macrophages, dendritic cells, and lymphocytes, and later the viral infection spreads to the epithelial cells of the trachea, lungs, oral cavity, pharynx, or intestines, which are SLAM-negative cells [66,67]. Another infection experiment using epithelial cell receptor-blind MV, demonstrated that the mutant MV inoculated intranasally to monkeys shows virulence and infectivity toward lymphoid tissues, although the virus cannot cross the airway epithelium and cannot be shed in the air [68]. The molecule forms tight junctions on polarized epithelial cells and was shown to function as the receptor for effectively releasing MV to the apical side of epithelial cells [69,70]. This explains why MV is highly contagious. Thus, the wild-type MV possesses two types of receptor, SLAM for entry and propagation and Nectin 4 for viral release into the air.

### 3.2. Structure of SLAMs of marine mammals

Cetaceans and sirenians have achieved complete adaptation to the aquatic environment and spend all of their lives in water. Cetaceans belong to the order Cetartiodactyla, superorder Laurasiatheria, and are closely related to hippopotami or ruminants among land animals. Sirenians, including dugongs and manatees, are in the order Sirenia, superorder Afrotheria, and are evolutionarily related to elephants or hyraxes. Pinnipeds, belonging to the order Carnivora, superorder Laurasiatheria, are not completely adapted to the aquatic environment and they must deliver and nurse their young on land. This characteristic of pinnipeds makes it possible to transmit infectious diseases between aquatic and land mammals. To determine the structure of marine mammal SLAMs, we collected blood samples from taxonomically different animal groups, i.e., cetaceans, pinnipeds, and sirenians. White blood cells were obtained from: two species of cetacean, a Pacific white-sided dolphin (*Lagenorhynchus obliquidens*) and a killer whale (*Orcinus orca*); two species of pinniped, a spotted seal (*Phoca largha*), and a walrus (*Odobenus rosmarus*); and a sirenian, a West Indian manatee (*Trichechus manatus*). The blood of an Indian elephant (*Elephas maximus bengalensis*) was also collected. After immune stimulation with phytohemagglutinin, RNAs of the leukocytes were extracted. First, the complete nucleotide sequences of the SLAM genes were determined. Three-dimensional models were then generated based on the deduced amino acid sequences to compare the interface of their SLAM V domains [71].

#### 3.2.1. Primary structure of SLAM proteins

The deduced amino acid sequences of marine mammal and elephant SLAMs indicated that they contain 336–339 amino acid residues, including six cysteine residues and six potential *N*-linked glycosylation sites (Figure 1). They have two immunoglobulin-like domains, V and C2, in the extracellular region, and two ITSM motifs (T-X-Y-X-X-V/I) and one ITSM-like sequence in the intracellular region. These molecular features are shared with all reported mammalian SLAMs (Figure 1). The cetacean and pinniped SLAMs showed the greatest homology with those of artiodactyla (cow and sheep, 84–85% identity at the amino acid level) and of dogs (84%), respectively. Manatee SLAM shared the greatest homology with that of the elephant (86%) [71].



SP: signal peptide, TM: transmembrane region, V: immunoglobulin V-like domain, C2: immunoglobulin C2-like domain. Closed squares: ITSM and ITSM-like motifs, The N-linked glycosylation site and cysteine residues are indicated by arrows and triangles, respectively.

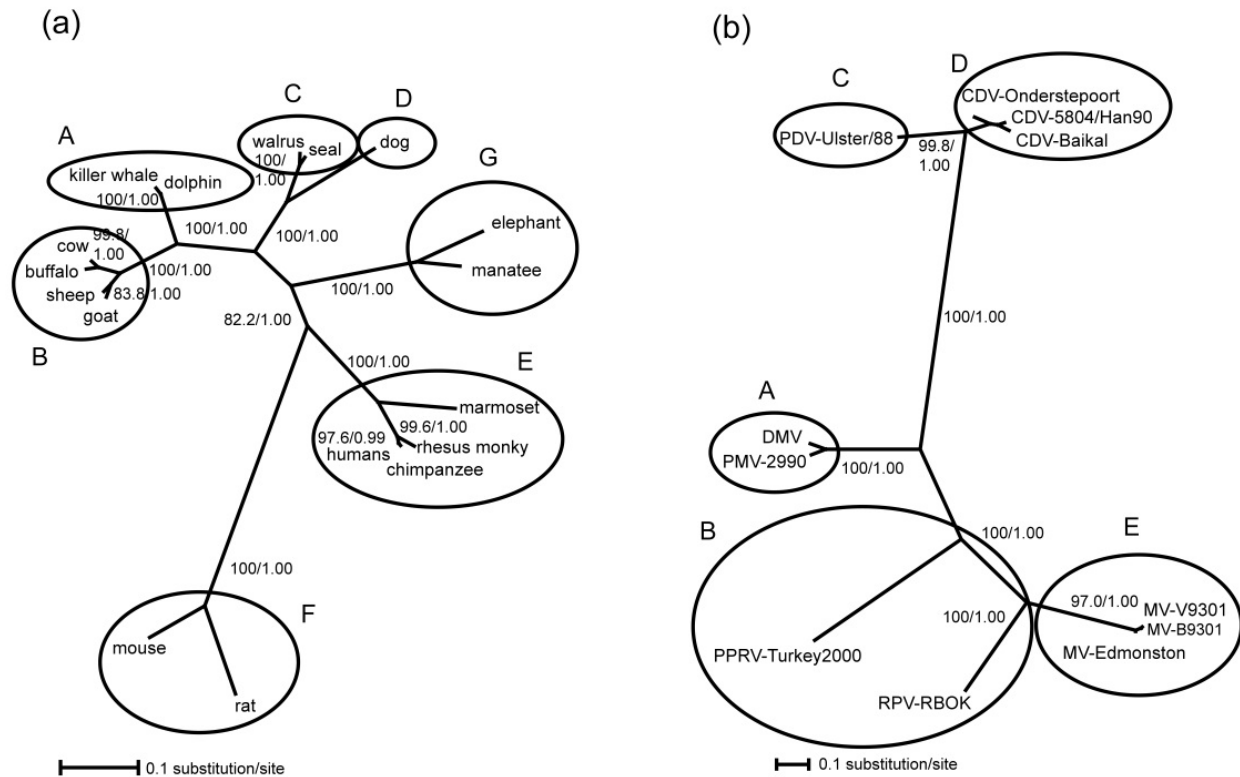
**Figure 1.** Schematic drawings of domain (a) and primary structure (b) of marine mammal SLAMs.

### 3.2.2. Phylogenetic analysis based on SLAM and morbillivirus H proteins

Phylogenetic trees based on SLAM and the morbillivirus H protein were constructed using the maximum-likelihood (ML) and Bayesian methods. In the phylogeny of SLAMs (Figure 2(a)), each taxonomic group, including primates (humans, chimpanzees, rhesus monkeys, and marmosets), cetaceans (Pacific white-sided dolphins and killer whales), artiodactyls (cows, buffalo, sheep, and goats), pinnipeds (spotted seals and walruses), and rodents (mice and rats), was monophyletic with a 100% ML bootstrap probability (BP) and a 1.00 Bayesian posterior probability (BPP). Manatee and elephant SLAMs, dog and pinniped SLAMs, and cetacean and artiodactyl SLAMs formed single clades, each with a 100% BP and a 1.00 BPP value, respectively.

Morbillivirus phylogeny based on MV H protein sequences reflected the host grouping, except for MV. CDV (dogs, Baikal seals) and PDV (seals), and PMV (porpoises) and DMV (dolphins), respectively, formed single clades each with 100% BP and 1.00 BPP support (Figure 2(b)). The monophyletic lineage of MV (human) (100% BP and 1.00 BPP) was within the grouping of ruminant viruses, RPV (cow) and PPRV (sheep and goat), with 100% BP and 1.00 BPP. These phylogenetic trees indicated that SLAMs and viral H proteins roughly co-evolved. However, the monophyletic lineage of MV and the ruminant viruses RPV and PPRV suggested that human MV may have originated from ancestral RPV in cattle by acquiring a binding affinity for human SLAM, as proposed in a previous report based on the morbillivirus P gene [9]





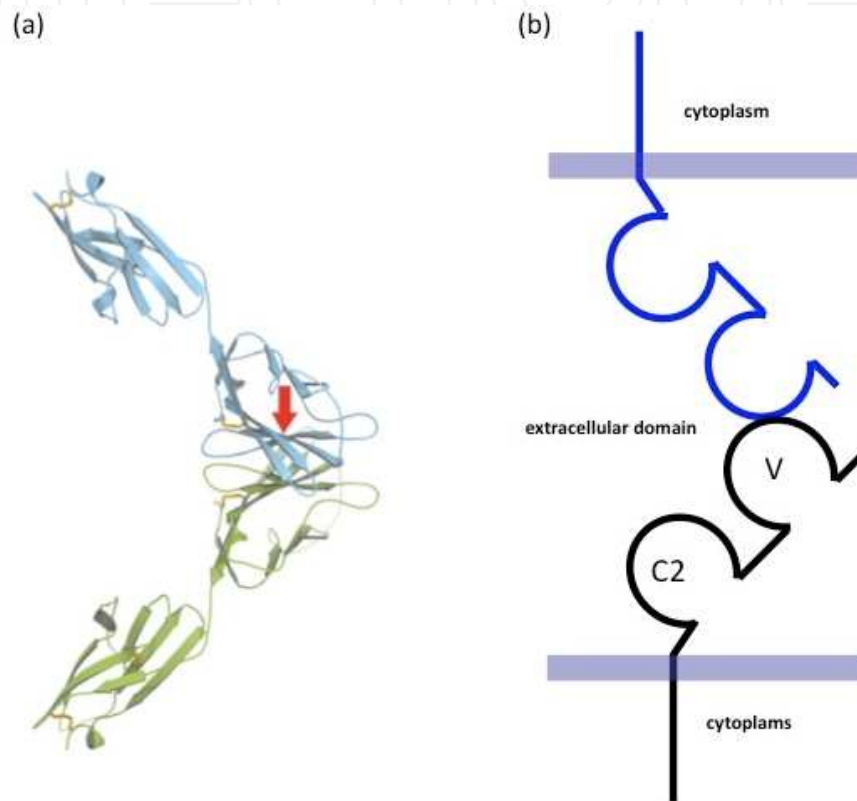
ML analyses were performed using PhyML [72], and an input tree was generated using BIONJ with the JTT model [73] along with amino acid substitution that incorporated invariable sites and used a discrete gamma distribution (eight categories) (JTT + I + G model). Bayesian phylogenetic analyses were conducted using MrBayes version 3.0 within the JTT + I + G model [74]. The ML bootstrap probabilities and BPPs are shown at the nodes. Host animals and the corresponding morbilliviruses are shown as circles with the same alphabetic notations: A, cetaceans; B, artiodactyla; C, pinnipeds; D, dogs; E, primates; F, rodents; and G, manatees and elephants. Morbillivirus has not been identified in rodents (F), or manatees and elephants (G). The following SLAM gene sequences were obtained from the Data Bank of Japan: Pacific white-sided dolphin (AB428366); killer whale (AB428367); spotted seal (AB428368); walrus (AB428369); Indian elephant (AB428370); American manatee (AB428371); human beings (*Homo sapiens*, NM\_003037); chimpanzee (*Pan troglodytes*, XM\_513924); marmoset (*Saguinus oedipus*, AF257239); Rhesus monkey (*Macaca mulatta*, XM\_001117605); cow (*Bos taurus*, AF329970); buffalo (*Bubalus bubalis*, DQ228868); sheep (*Ovis aries*, NM\_001040288); goat (*Capra hircus*, DQ228869); dog (*Canis familiaris*, AF325357); mouse (*Mus musculus*, NM\_013730); and rat (*Rattus norvegicus*, XM\_001054873). Morbillivirus H protein sequences were obtained as follows: MV Edmonston AIK-C strain (AB046218); MV V9301 strain (AB012948); MV B9301 strain (AB012949); RPV RBOK strain (Z30697); PPRV Turkey 2000 strain (NC\_006383); CDV Onderstepoort vaccine strain (AF305419); CDV Baikal seal strain (X84998); CDV 5804/Han90 strain (X85000); PDV Ulster/88 strain (D10371); PMV 2990 strain (AY586537); and DMV (NC\_005283). The alignments of the deduced amino acid sequences from these genes were generated using ClustalW version 1.8, inspected visually, and edited manually. This figure was adapted from [71].

**Figure 2.** Phylogenetic trees of SLAM peptide sequences (a) and morbillivirus H proteins (b).

### 3.2.3. Three-dimensional models of marine mammal SLAM extracellular domain

In order to analyze the binding site for morbillivirus, three-dimensional (3D) models of marine mammal SLAM extracellular domains were generated by homology modeling. Previously, we constructed 3D homology models based on the crystallographic structure of the human NTB-A molecule, a member of the SLAM family, as a template [71,75]. In the present study, we generated a new version of the models by adding the recently determined

crystal structure information of the bound complex of MV H and marmoset SLAM V [56]. Figure 3 shows the 3D model of the Pacific white-sided dolphin SLAM extracellular domain in a self-ligand form. In the models, the V and C2 domains are shown with rod-like structures, which are both constituted mainly of  $\beta$ -sheets containing several  $\beta$ -strands. The cysteine residues appear to be important in forming the basic 3D structures. On the basis of amino acid sequence similarity, this structure is shared with all of the SLAMs examined. The V domain possesses a two-layered  $\beta$ -sheet structure, and the front sheets provide an interface for binding with morbilliviruses.

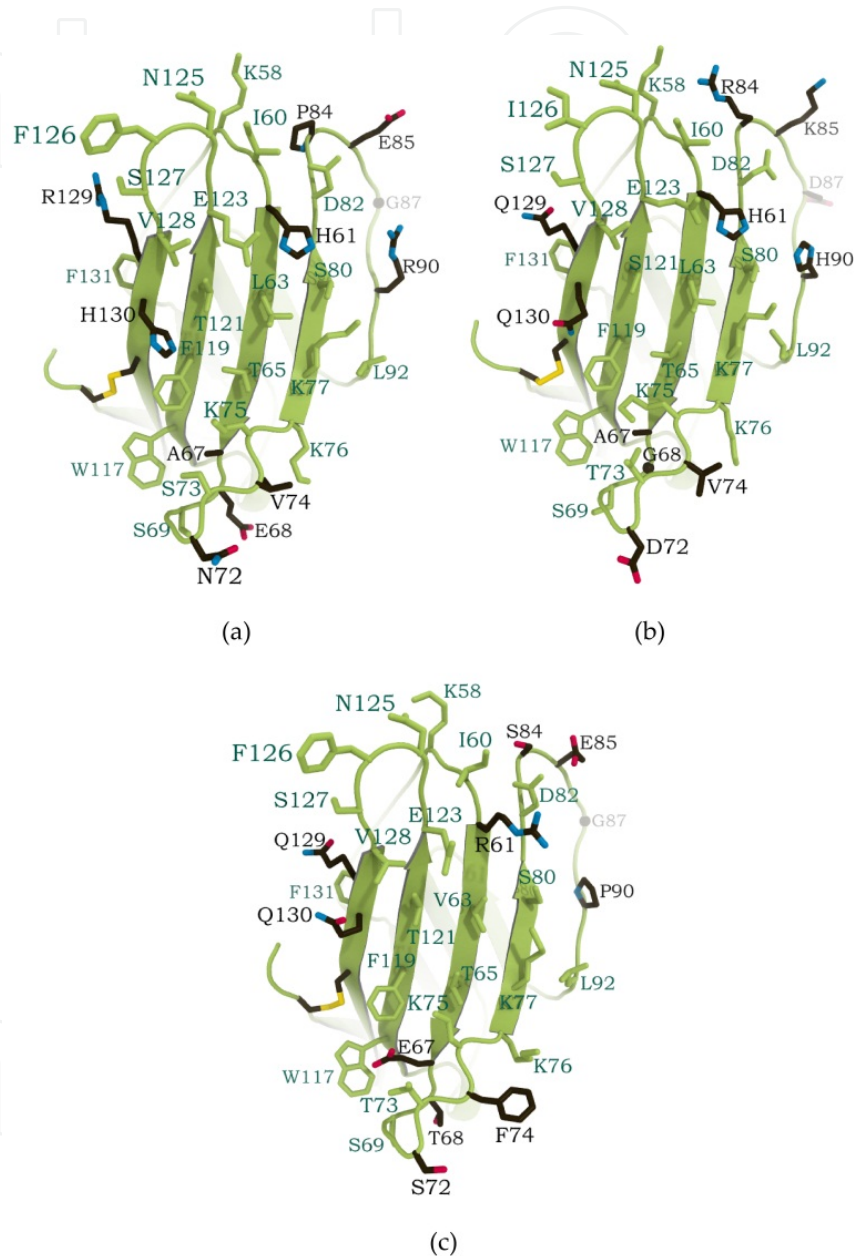


In (a), the blue and green models show respective SLAM extracellular domains forming a homophilic dimer. The  $\beta$ -strands are indicated by arrows and the disulfide bonds are shown as yellow bars. The thick red arrow indicates the direction of view of the front face of the morbillivirus binding site, as shown in Figure 4. In (b), the blue and black models indicate two SLAM molecules of two adjacent cells, respectively. The Protein Data Bank (PDB) entries for the marmoset SLAM in the complex (3ALW: A-D chains, 3ALX: A-D chains, 3ALZ: B chain; reference [56]) and for human NTB-A (21F7: A-D chains; reference [75]), were used as the template structure. The 3D model was constructed using the MODELLER 9.10 program [76] and visualized using PyMOL 1.4.1 (Schrodinger LLC) and PovRay (Persistence of Vision Pty. Ltd.).

**Figure 3.** Ribbon diagram of the 3D structure (a) and schematic drawing (b) of the SLAM extracellular domain from the Pacific white-sided dolphin.

Figure 4 shows top views of the front face of the modeled V domains of SLAMs of the spotted seal, Pacific white-sided dolphin, and West Indian manatee. The amino acid residues that have protruding side-chains on their front faces are likely a component of virus binding. We found such qualified 27 amino acid residues; 12 amino acid residues on the  $\beta$ -strands and 15 residues on loops (Figure 4). In addition, the amino acid residues positioned at 76, and the residues at 127-131 are thought to be important for the binding of

the virus, because the side-chains of these residues are closely located to those of viral H protein in a crystal structure of the complex [56]. Particularly, the residues at 127-131 are thought to form an intramolecular  $\beta$ -sheet with the  $\beta$ -strand of MV H [56]. The overall 3D structures of the interfaces are similar among SLAMs, but several among the total 32 amino acid residues possibly contributing the binding affinity to the virus, differed among the three marine mammals.



The interfaces are viewed from the direction shown by the thick red arrow in Figure 3. The amino acid residues that possibly interact with the viral H protein, are shown with their position numbers. The different amino acid residues among the three mammal SLAMs are indicated in black, and their side-chains are shown with the atoms colored (black for carbons, blue for nitrogens, and red for oxygens). The shared residues among the three are shown in blue. Disulfide bonds are shown in yellow.

**Figure 4.** Ribbon diagram of the 3D structure models of the SLAM interface for binding morbillivirus from the spotted seal (a), Pacific white-sided dolphin (b), and manatee (c).

### 3.2.4. Prediction of amino acid residues involved in virus binding and host–virus specificity

To identify amino acid residues that are important for host–virus specificity, we compared the 32 residues with those of land mammal SLAMs (Table 2). The difference in the SLAM interface was only two amino acid residues between seal and dog (Val and Ile at position 74, and Arg and Gln at position 129), between human and marmoset (Leu and Phe at position 119, Val and Ile at position 126, marmoset data not shown), and between cow and sheep (Asp and Gly at position 87, and Arg and His at position 90). This is consistent with the evidence that mass die-offs of Baikal seals and Caspian seals were caused by CDV; marmosets are highly sensitive to MV; and that RPV and PPRV can infect ruminants. It is noted that the identity of these 32 residues between dolphin and cow SLAMs is very high, although they are infected by different morbilliviruses, CMV and RPV, respectively. Four residues are different between the two animals, while eleven and fourteen residues are different between dolphin and seal, and between dolphin and humans, respectively.

a.a. No.	Seal	Dog	Dolphin	Cow	Sheep	Human	Manatee
58	K	K	K	K	K	K	K
60	I	I	I	I	I	I	I
61	H	H	H	H	H	H	R*
63	L	L	L	L	L	V	V
65	T	T	T	T	T	T	T
67	A	A	A	A	A	A	E*
68	E	E	G*	E	E	K*	T*
69	S	S	S	S	S	S	S
72	N	N	D	D	D	N	S
73	S	S	T	T	T	S	T
74	V	I	V	V	V	V	F
75	K	K	K	K	K	E*	K
76	K	K	K	K	K	N*	K
77	K	K	K	K	K	K	K
80	S	S	S	S	S	S	S
82	D	D	D	D	D	D	D
84	P	P	R	R	R	S	S
85	E	E	K	K	K	E	E
87	G	G	D	D	G	G	G
90	R	R	H	R	H	R	P*
92	L	L	L	L	L	L	L
117	W	W	W	W	W	W	W
119	F	F	F	F	F	L	F
121	T	T	S	S	S	T	T
123	E	E	E	E	E	E	E

a.a. No.	Seal	Dog	Dolphin	Cow	Sheep	Human	Manatee
125	N	N	N	N	N	N	N
126	F	F	I	V	V	V	F
127	S	S	S	S	S	S	S
128	V	V	V	V	V	V	V
129	R*	Q	Q	Q	Q	Q	Q
130	H	H	Q	H	H	R	Q
131	F	F	F	F	F	F	F
Viruses	PDV, CDV	CDV	CMV	RPV, PPRV	PPRV, RPV	MV	None

The residue position, which varies among animals, is shaded. The light- and dark-shaded boxes indicate a variation in chemically (charge, hydrophilicity, etc.) similar or different residues. The asterisk indicates the specific residue with a chemical change for the animal SLAM. See the legend of Figure 2 for the animal names and accession numbers of the amino acid sequences used in this table.

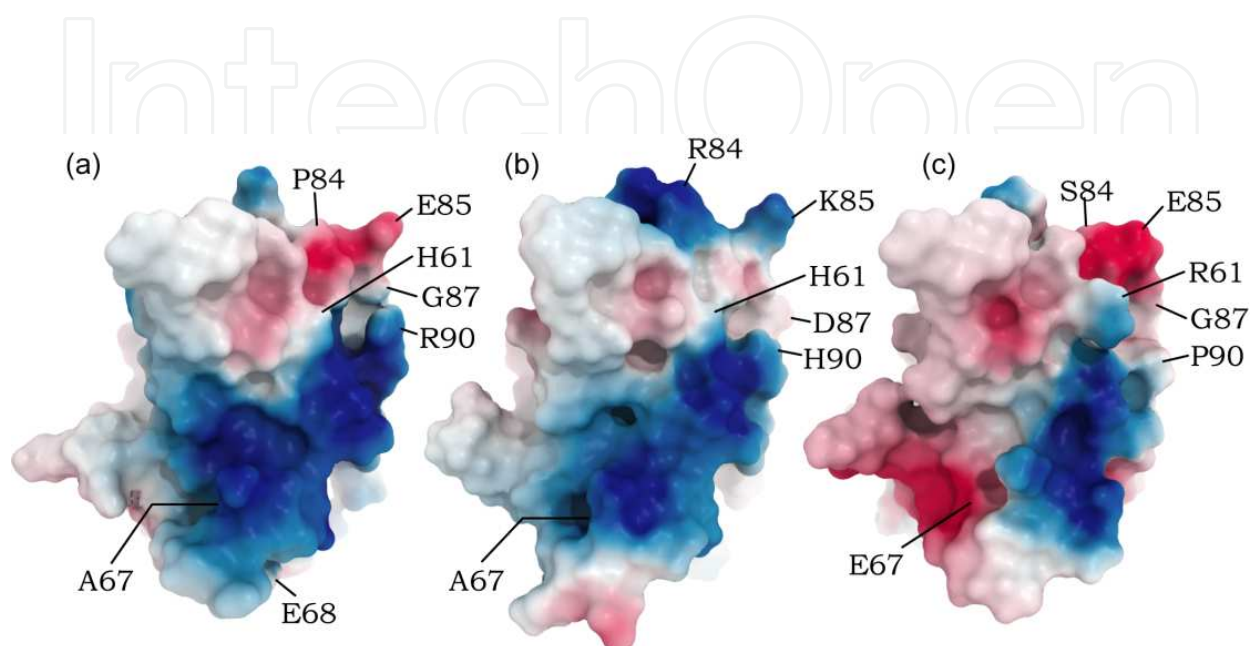
**Table 2.** Amino acid residues on the SLAM interface possibly involved in regulating the binding and specificity of morbilliviruses.

Among the 32 residue positions, variations in amino acids were found at 18 positions (Table 2, light and dark shading). At six positions (63,73,74,119,121, and 126), the changes are between chemically similar residues (light-shaded boxes in Table 2) and these do not seem to markedly affect binding with the viruses. On the other hand, the variations at the other twelve residue positions (61,67,68,72,75,76,84,85,87,90,129, and 130; dark-shaded boxes in Table 2) occur in amino acids with chemically different characteristics. In particular, the variations among amino acids with opposite charge may significantly alter the affinity for viruses (positions 68,75, and 85). The twelve amino acid residues are thought to be important in determining host–virus specificity. Almost of the twelve residues are located in the edge region of the interface. This may indicate that residues located in the central region of the interface play an important role in virus entry itself, rather than in host–virus specificity. Alternatively, they may be essential for a primary immunological function.

A detailed binding assay using surface plasmon resonance analysis was carried out between human SLAM mutants and the MV H protein [56,57]. The respective changes in the residues from H61, E123, and R130 of the human SLAM interface to serine residues completely abolished the binding ability to the MV H protein. In crystallographic analysis, R130 was suggested to form an intramolecular salt bridge with E75 [56]. Only human SLAM possesses these two residues on the interface. As shown in Table 2, K68, a strong positively charged residue, is also specific for human SLAM. These facts suggest that they are key residues for MV infection. On the other hand, H61 and E123 are conserved in all mammals, except for R61 of manatees, suggesting that these residues play a crucial role in viral infection, rather than in host–virus specificity.

Although a detailed analysis of SLAM–virus interaction has not been conducted in systems other than the human SLAM–MV complex, animal-specific residues can be seen in Table 2. For example, the markedly specific residue set R84–K85–D87–H90 is found in dolphin. These

residues are located spatially near each other in the 3D homology model of the interface (Figure 4). To clarify the influence of the changes in the charge, electrostatic potentials on the surface of SLAM interfaces of the three marine mammals, are shown in Figure 5. It can be seen that the zone constituted by the residues at positions 84, 85, 87, and 90 are different among the SLAM interfaces of three marine mammals.



Electrostatic potential was calculated using DelPhi v.4 [77,78]. Positively and negatively charged surfaces are colored blue and red, respectively.

**Figure 5.** Electrostatic potential on the surface of the SLAM interfaces with morbilliviruses deduced from the 3D homology model structures of the SLAM interfaces from the spotted seal (a), Pacific white-sided dolphin (b), and manatee (c).

The amino acid residues at positions 67 and 68 are also highly variable among the three interfaces (Table 2). The manatee-specific residue E67 appears to contribute greatly to the formation of the negatively charged zone (Figure 5). The manatee SLAM has two another specific residues, R61 and P90, which induce an acquisition of stronger positive charge or a loss of positive charge on the interface (Table 2, Figure 4). These findings suggest that if there is a morbillivirus for the sirenians, it has the H protein with a very different SLAM binding interface.

Crystallographic analysis of the complex of MV H and marmoset SLAM V unexpectedly showed two different potentially tetrameric configurations, form I and form II [56]. Residue N53 is located at the interface only in form II. Its replacement mutant changing to Q53 showed a reduction in molecular masses, meaning the loss of glycosylation, and an unexpected increase in MV entry into human cells. The reason for this is not fully understood. However, because only primate and manatee SLAMs possess residue N53, it may also be involved in host-virus specificity.

#### **4. Risk assessment of morbillivirus infection based on SLAM interface structures**

Human beings have a long history of diseases caused by morbilliviruses, which introduced devastating contagious diseases to humans and domestic animals. Since Jenner's seminal discovery of the concept of immunity and vaccines, vaccines against various pathogens have been developed. By virtue of that great endeavor, an effective vaccine against measles is now available [79,80]. It has reduced measles deaths worldwide by 74% between 2000 and 2010 (from 535,300 to 139,300), although measles is still a threat for children in developing countries [81]. Rinderpest induced by RPV, one of the oldest recorded livestock plagues, has been actually eradicated by the success of the Global Rinderpest Eradication Programme [82-84]. Thus, numerous efforts at eradication have achieved the control of human and domesticated animal diseases. Similar control of morbillivirus infections in wild animals will be one of the most important issues in the field of veterinary medicine in the 21st century. Marine mammals have large geographical ranges in the oceans. For example, baleen whales are known to migrate seasonally from the equator to the polar seas, indicating that they may be a dynamic vector for infectious diseases. In addition, recent global climate change may alter the ecology of marine mammals, such as their habitats, migration patterns, food, and behavior, and may increase opportunities for contact among previously geographically separate mammalian populations. These alterations may increase the possibility of viral transmission and the likelihood of outbreaks in susceptible mammalian populations.

In viral infection, disease incidence, and transmission, several factors in host cells play a key role. In addition, ecological factors such as animal distribution, population structure and size, and behavior are decisive factors in actual infection. In the present study, we used a new approach to assess the potential infectivity of morbilliviruses based on receptor structure predictions. The residues on the interface of the SLAM V domain probably contribute to virus binding, and some residues among them are key for host-virus specificities. The analysis of these residues on 3D models of the SLAM receptor is useful for estimating the risk of morbillivirus infection in wild animals. This approach is applicable to animals for which no information on infection and disease. For the animals, it is possible to predict potential infection with known morbilliviruses. This may reveal possible infection spectra of morbilliviruses and suggest which mammals are reservoirs that maintain the viruses and how these viruses spread among wild mammals in nature.

Control of infectious diseases in wild animals is very difficult. However, even though we cannot stop outbreaks from occurring in nature, information on the potential sensitivity of wild mammals against a virus may minimize the damage or prevent the spread of disease by such means as artificial transportation. Because marine mammals are positioned at the top of oceanic food chain, a decrease in marine mammal populations will affect marine ecosystems. We believe that the present study contributes to the conservation of marine mammals and their ecosystems.

## 5. Conclusion

Morbillivirus, a member of the family Paramyxoviridae, is a causative agent of mass mortalities of marine mammals. To date, four virus species, MV, RPV, PPRV, and CDV have been identified in land mammals, and two virus species, PDV and CMV, have been identified in seals and cetaceans, respectively [4,47]. The notable biological feature of morbillivirus is its high level of host specificity. The cellular receptor for a virus is a major determinant of its host specificity and tissue tropism. SLAM is the principal cellular receptor for morbilliviruses allowing entry and propagation [18,19]. SLAM contains two immunoglobulin-like domains, the V and C2 domains, in the extracellular region. The morbillivirus H protein binds to the V domain on the target cells, which triggers viral infection [53]. To assess the host-virus specificity of morbillivirus in marine mammals, we determined the complete nucleotide sequences of SLAM from five species belonging to cetaceans, pinipeds, and sirenians, and generated 3D homology models. The results showed that the overall structures are similar in the mammals examined. We found 32 amino acid residues on the interface of SLAM V domain that are potentially involved in the interaction with viruses. Among them, a set of 18 amino acid residues is important for morbillivirus binding because some residues in the set differ among the mammal groups, which are susceptible to different morbillivirus species. A change in some residues in the set may cause an electrostatic change on the interface surface. These amino acid residues are thought to be important for host-virus specificity.

Analysis of these residues on the interfaces of SLAMs will be useful to assess the risk of morbillivirus infection in wild animals. Recent climate change may increase the opportunities for new contacts among wild mammals and for the transmission of viruses. In the present study, we propose a new approach to assess the viral sensitivities of wild mammals by analyzing the host receptors. This approach will contribute to the conservation of wildlife including marine mammals and ecosystems.

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