FELINE INFECTIOUS PERITONITIS

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Feline Infectious Peritonitis: The causative virus, viral mutations, transmission, disease outcomes and treatments, prevention.

LECTURE OUTLINE

- What is Feline Infectious Peritonitis?
- RNA viruses
- Coronaviruses
- Feline coronavirus morphology
- Spike proteins
- Feline coronavirus mutations
- Pathogenesis of FIP

Patient age

Role of Macrophages/Monocytes in FIP

Forms of FIP: Dry/Wet/Combination

Transmission of FIP?

Disease outcomes: Historical, Current

Diagnostic Testing

Disease prevention: Vaccines? Husbandry?

Current “legal” treatments

Currently available treatments

What does the future hold?

Table 1

Prevalence, odds ratios, and confidence intervals for purebreed cats with feline infectious peritonitis (FIP)

Breed[a]	Cats diagnosed with FIP/total number cats seen (% affected with FIP)	Odds ratio	Confidence interval	*P*-value (Fisher's exact test)
Abyssinian	3/99 (3.0%)	8.98	2.71–29.77	0.006
Bengal	1/8 (12.5%)	41.03	4.91–342.85	0.028
Birman	4/18 (22.2%)	82.06	26.66–262.44	<0.001
Burmese	1/37 (2.7%)	7.98	1.06–59.91	0.124
Exotic Shorthair	1/62 (1.6%)	4.71	0.63–34.98	0.199
Havana Brown	2/2 (100%)	_[b]	_[b]	_[b]
Himalayan	4/364 (1.1%)	3.19	1.12–9.06	0.046
Manx	1/67 (1.5%)	4.35	0.59–32.29	0.213
Persian	4/481 (0.5%)	2.41	0.85–6.83	0.101
Ragdoll	2/13 (15.3%)	52.22	11.14–244.79	0.001
Rex (Cornish and Devon)	2/17 (11.7%)	38.29	8.42–174.15	0.002
Russian Blue	1/39 (2.6%)	7.56	1.01–56.68	0.130
Siamese	1/536 (0.2%)	0.54	0.07–3.93	1.00

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The story of Feline Infectious Peritonitis is a tale of

- Virus Sleeper Cells
- A shape shifting RNA virus
- Hijacking
- Militaristic adventurism
- “Turncoats and Trojan Horses”
- Commandering the means of production and reproduction in host cells
- Stealth
- Invisible drone-like strikes
- Mass suicide/Apoptosis of the opposing forces
- Attrition of the host defences
- Panic
- Host internal climate crisis
- Floods
- Desertification
- Greed
- Apocalypse

Introduction

What is Feline Infectious Peritonitis?

Feline infectious peritonitis (FIP) was described as a specific disease entity in 1963 by veterinarians at the Angell Memorial Animal Hospital in Boston (Holzworth 1963)

THE VIRUS

- Feline enteric coronavirus is essentially a go along to get along virus
- Causes minimal clinical clinical signs if any
- Rapidly transmitted by fecal oral route
- Reside in the enterocytes of the lower intestines
- Specific mutations of the coronavirus enables it to escape the enterocyte and invade macrophages
- This escape takes place in 10 percent of infections
- The infection of macrophages is eliminated in all but 0.3 to 1.4 % of cats
- The initial site of disease is the lymphoid tissue of the proximal colon, cecum and lower small intestines

PREDISPOSING CONDITIONS

- Young age
- Genetic susceptibility
- Sex
- Overcrowding
- Poor nutrition
- Stressful events

RNA VIRUSES

- Utilize ribonucleic acid in their genetic structure
- Prone to mutations
- RNA virus replication include high
  - mutation rates, high yields, and short replication times
- RNA viruses replicate as complex and dynamic mutant swarms.

CORONAVIRUSES

Alpha Coronoviruses

Beta Coronaviruses

Gamma Coronaviruses

Delta Coronaviruses

- Coronaviruses are enveloped, single-stranded positive-sense RNA viruses
- The surface of each virus is has glycoprotein spikes that bind to host receptors
- On entering the host cell the virus is dismantled releasing its genetic material
- Viral RNA is replicated multiple times and new virus is reassembled utilizing the Golgi bodies and Endoplasmic reticulum of the host cell.
- The newly formed viruses are then secreted from the host cell, ready to infect other cells

- .

CORONAVIRUSES

Alpha Coronoviruses include the Feline Coronavirus,Canine Coronavirus and recombinants of these.

Beta Coronaviruses include the SARS Coronavirus and MERS Coronavirus

NOMENCLATURE

- FCoV Feline Coronavirus
- FECV Feline Enteric Coronavirus
- FIP Feline Infectious Peritonitis Virus

FCoV Infection Rate : 80 – 90 % in animal shelters

- Fecal Oral Transmission
- The transmission in shelter facilities is rapid
- 60 % of newly admitted kittens were shedding FCoV within a week of admission
- Shared litterboxes are a prime venue for transmission
- Cats infected with FCoV can shed the virus intermittently
- The virus has a high degree of affinity for epithelial cells
- It inhabits the enterocytes
- Causes damage to the tips of the villi
- Causes self limiting diarrhea which is often subclinical

COMMON VIRUS INFECTIONS IN CATS, BEFORE AND AFTER BEING PLACED IN SHELTERS, WITH EMPHASIS ON FELINE ENTERIC CORONAVIRUS.

LANGUAGE: ENGLISH
J FELINE MED SURG. APRIL 2004;6(2):83-8.

N C PEDERSEN 1, R SATO, J E FOLEY, A M POLAND

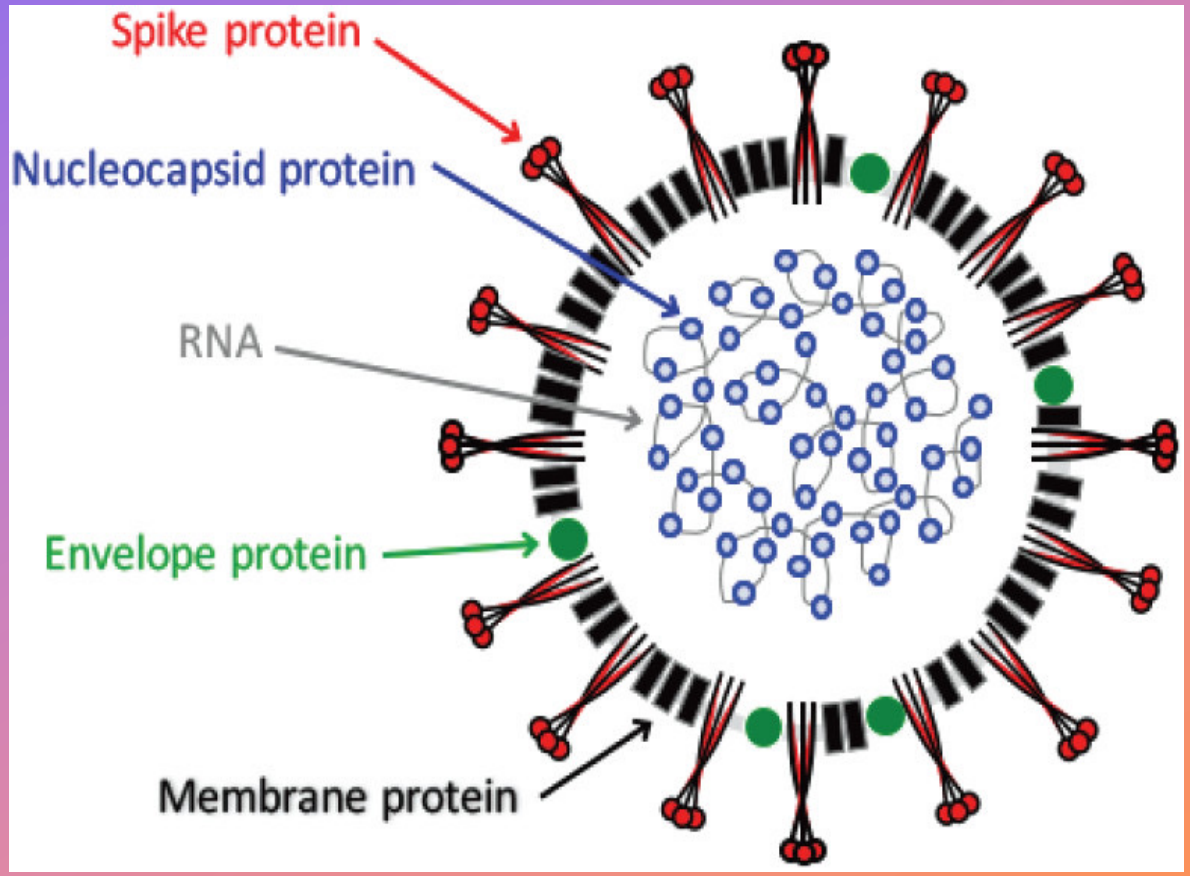
ARTICLE ABSTRACT

THE PURPOSE OF THIS STUDY WAS TO DETERMINE THE ORIGIN AND SUBSEQUENT SPREAD OF FELINE CALICIVIRUS (FCV), FELINE HERPESVIRUS (FHV), AND FELINE ENTERIC CORONAVIRUS (FECV) IN CATS RELINQUISHED TO SHELTERS. FCV WAS ISOLATED FROM THE ORAL FAUCES OF 11% OF HEALTHY CATS UPON ENTRY, AND ISOLATION RATES WERE HIGHEST FOR KITTENS (33%). FHV SHEDDING WAS VERY LOW (4%) AT THE TIME OF ENTRY AND OCCURRED MAINLY IN JUVENILES. FECV SHEDDING WAS ALSO COMMON AMONG NEWLY RELINQUISHED CATS (33%), ESPECIALLY OLDER KITTENS AND JUVENILES (90%). THE SUBSEQUENT SPREAD OF ALL THREE VIRUSES WAS RAPID AND EFFICIENT IN THE SHELTER ENVIRONMENT. FIFTEEN PERCENT OF CATS WERE SHEDDING FCV, 52% FHV, AND 60% FECV AFTER 1 WEEK. **MORE DETAILED STUDIES WERE DONE WITH FECV SHEDDING, WHICH COULD BE ACCURATELY QUANTITATED. THE AMOUNTS OF FECV SHED BY INFECTED CATS RANGED FROM 10(2)TO 10(16)PARTICLES/SWAB OF FECES. FECV SHEDDING WAS SEVERAL LOGS HIGHER IN YOUNG KITTENS WITH PRIMARY INFECTION THAN ADULT CATS WITH PRIMARY INFECTIONS.**

FELINE CORONAVIRUS MORPHOLOGY

Two Serotypes

- Type 1: Most common in Europe and America
- Type 2: Recombinant Canine and Feline coronavirus most commonly found in Asia



SPIKE PROTEINS

FELINE CORONAVIRUS MUTATIONS

- All mutations not currently known
- RNA viruses are prone to mutations
- The mutation changes the focus/tropism of the virus from enterocytes, to monocytes and macrophages

FELINE CORONAVIRUS MUTATIONS

Outbreak of feline infectious peritonitis (FIP) in shelter-housed cats: molecular analysis of the feline coronavirus S1/S2 cleavage site consistent with a 'circulating virulent-avirulent theory' of FIP pathogenesis.

Language: English
JFMS Open Rep. 2022 Jan-Jun;8(1):2055116922107422 6.

Eleni A Healey 1, Nicole M André 2, Andrew D Miller 3, Gary R Whittaker 2, Elizabeth A Berliner 4

Article Abstract

CASE SERIES SUMMARY:This case series describes three shelter-housed cats concurrently diagnosed with feline infectious peritonitis (FIP). The cats were from a cohort of seven surrendered from the site of a house fire. The three cats presented with mild upper respiratory signs. Within 10 days they clinically declined: progressive signs included pyrexia, icterus, lethargy, anorexia and cavitary effusions. Necropsy followed by histopathology and immunohistochemistry confirmed a diagnosis of FIP in all three. **Molecular analysis of the causative feline coronavirus (FCoV) revealed varied amino acid alterations in the spike gene both between cats and between sample types in individual cats.** A fourth cat from the cohort remained healthy in the shelter but succumbed to FIP 6 weeks post-adoption.

FELINE CORONAVIRUS MUTATIONS

RELEVANCE AND NOVEL INFORMATION:

This case series places FCoV genetic sequences in the context of clinical signs in a small shelter outbreak. Each of the three cats concurrently developed a slightly different clinical presentation. PCR amplification and genetic sequencing revealed that two cats shared an S1/S2 cleavage site mutation (R790S) previously described to be associated with the development of FIP; one of the cats had an additional S1/S2 cleavage site mutation (R793S). The third cat had a single, identical S1/S2 point mutation (R790G) unique from the other two cats; the R790G mutation has not been previously reported. This case series provides interesting data on point mutations associated with the development of FIP and provides support for a 'circulating virulent-avirulent theory' of FIP pathogenesis in a small shelter outbreak.

Cryo-EM analysis of a feline coronavirus spike protein reveals a unique structure and camouflaging glycans

Tzu-Jing Yang [1,2], Yen-Chen Chang [1,3], Tzu-Ping Ko [1], Piotr Draczkowski [1], Yu-Chun Chien [1,2], Yuan-Chih Chang [4], Kuen-Phon Wu [1], Kay-Hooi Khoo [1,2], Hui-Wen Chang [5], Shang-Te Danny Hsu [6,2]

Abstract

Feline infectious peritonitis virus (FIPV) is an alphacoronavirus that causes a nearly 100% mortality rate without effective treatment. Here we report a 3.3-Å cryoelectron microscopy (cryo-EM) structure of the serotype I FIPV spike (S) protein, which is responsible for host recognition and viral entry.

Mass spectrometry provided site-specific compositions of densely distributed high-mannose and complex-type N-glycans that account for 1/4 of the total molecular mass; most of the N-glycans could be visualized by cryo-EM. Specifically, the N-glycans that wedge between 2 galectin-like domains within the S1 subunit of FIPV S protein result in a unique propeller-like conformation, underscoring the importance of glycosylation in maintaining protein structures. The cleavage site within the S2 subunit responsible for activation also showed distinct structural features and glycosylation. These structural insights provide a blueprint for a better molecular understanding of the pathogenesis of FIP.

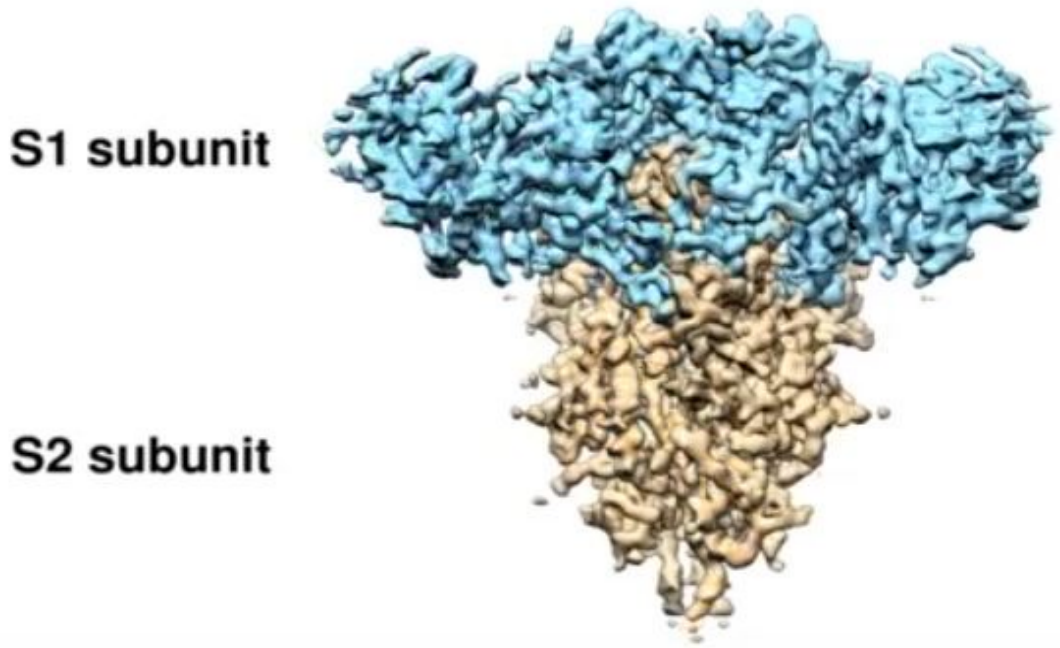
- CoVs use their spike (S) proteins for host recognition and subsequent membrane fusion to introduce their viral genomes into the host for replication.
- Preventing CoV infection by blocking S-protein binding to host receptors therefore represents the first line of defense.
- CoV S proteins consist of 2 functional units, the S1 and S2 subunits, which are responsible for cell attachment and membrane fusion, respectively (1, 2, 15).
- Mutations in the receptor-binding motifs (RBMs) or cleavage sites of CoV S proteins can lead to zoonotic spillover and alteration of cell/tissue tropism, as exemplified by SARS and MERS (1, 16).

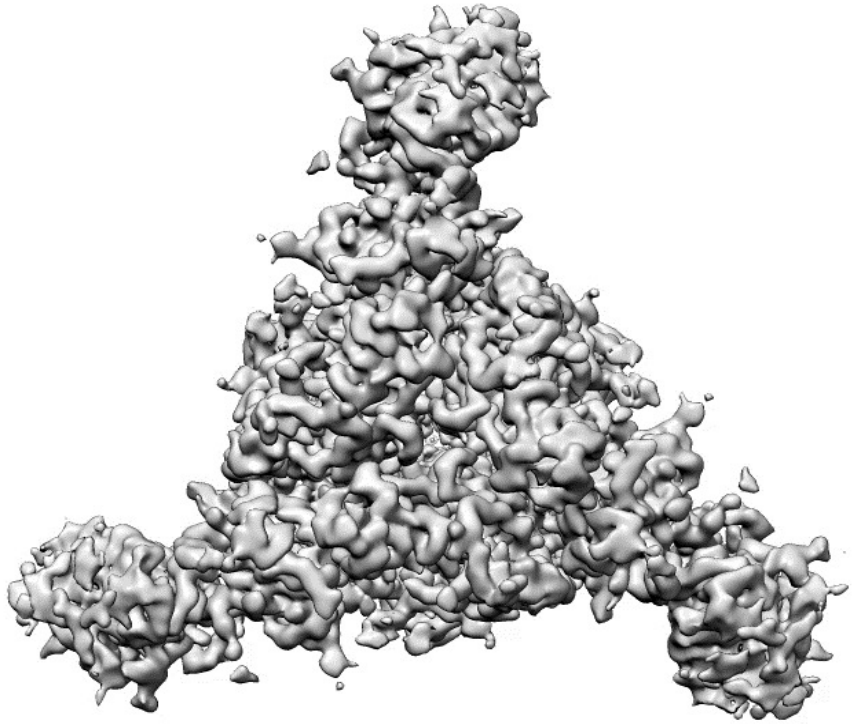
•. 2020 Jan 21;117(3):1438-1446.
doi: 10.1073/pnas.1908898117. Epub 2020 Jan 3.

SPIKE PROTEIN STRUCTURE

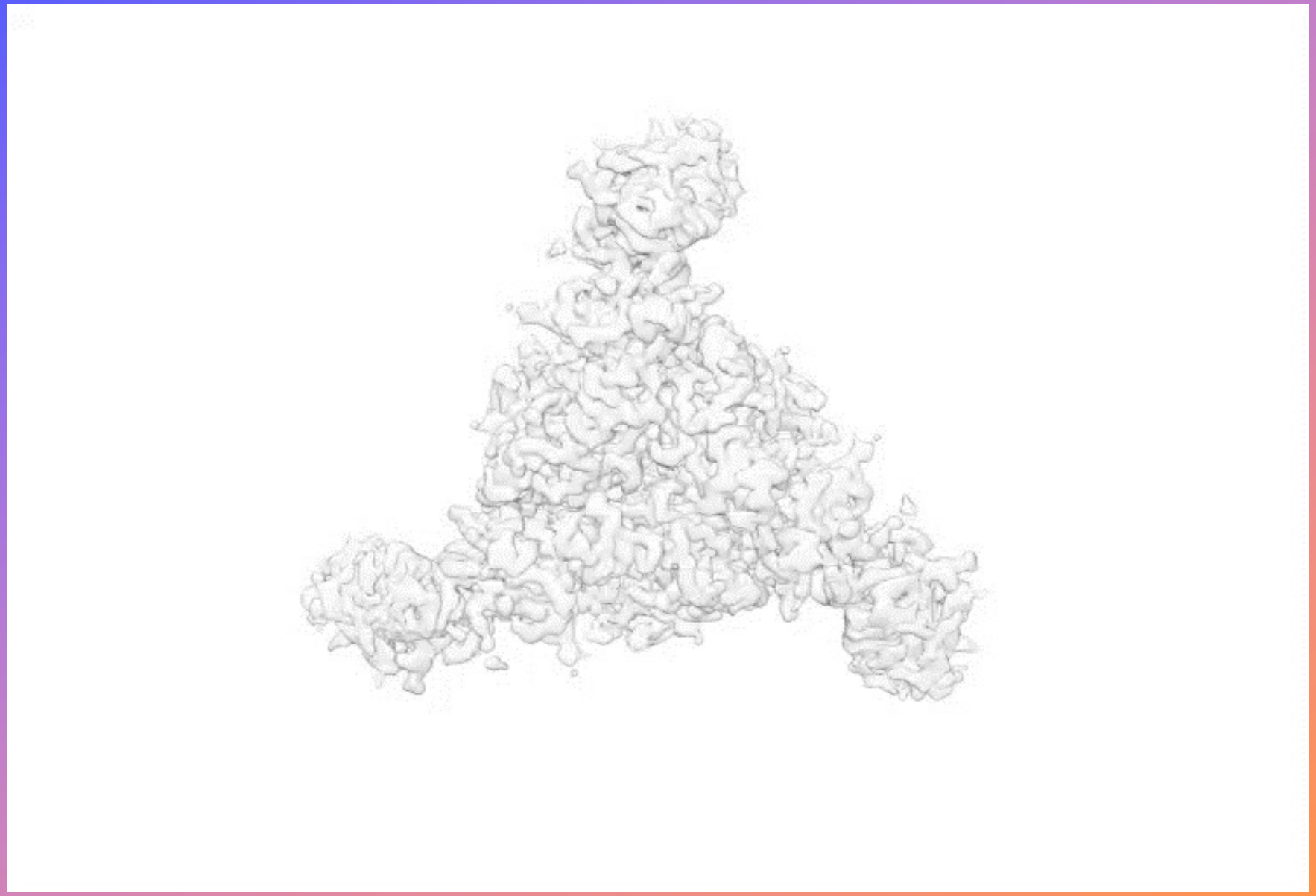
There exist 3 N-glycans that wedge between 2 galectin-like domains within the S1 subunit of FIPV-UU4 S protein, resulting in a propeller-like conformation unique to all reported CoV S proteins. The results highlight a structural role of glycosylation in maintaining complex protein structures.

Structure of FIPV-UU4 S Protein.





Mapping *N*-glycosylation of FIPV-UU4 S protein by MS and cryoEM.

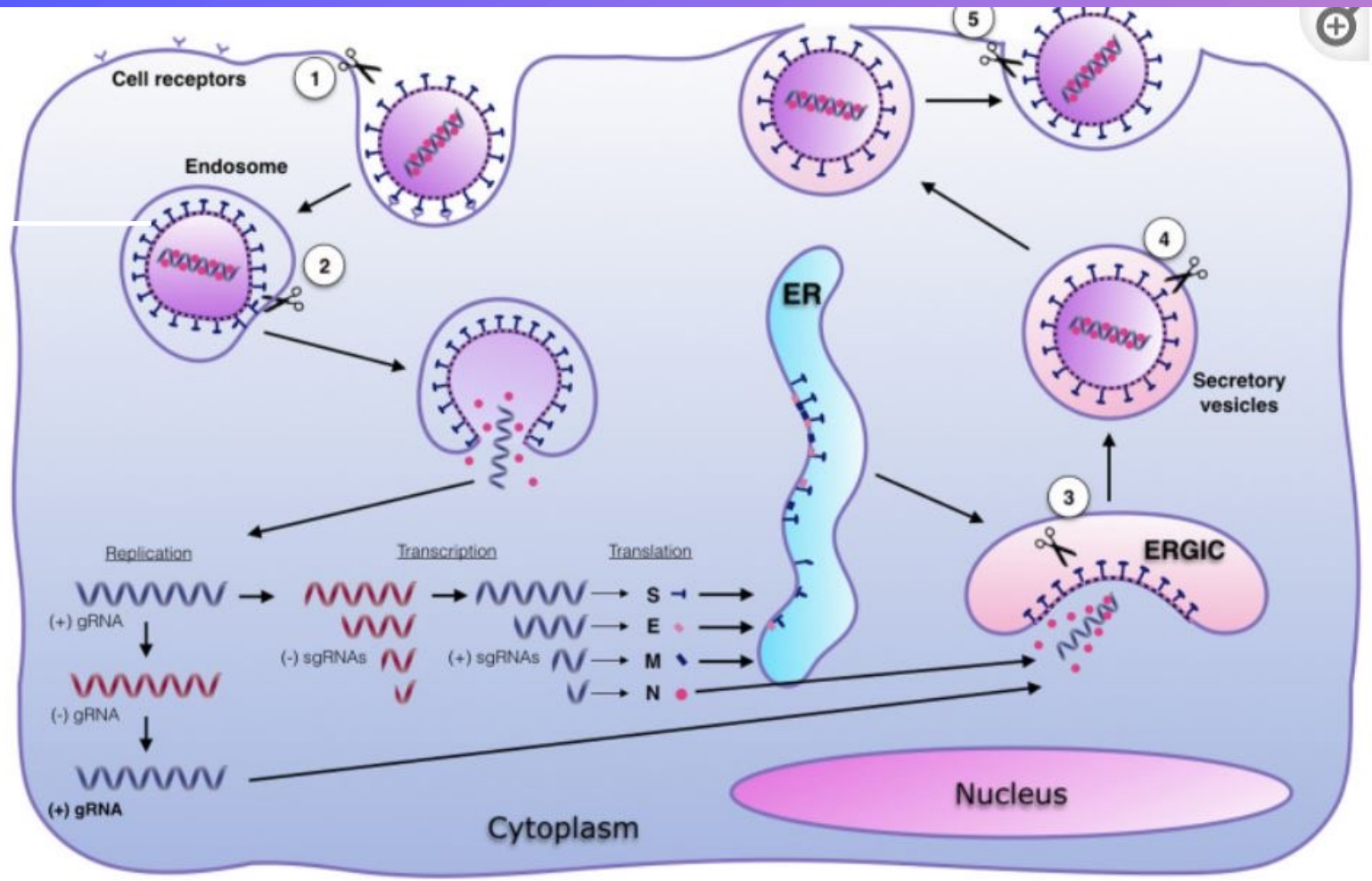


Mutations To Virulence

Two amino acid substitutions, M1058L and S1060A, within the spike protein have been associated to the FECV/FIPV virulence change.

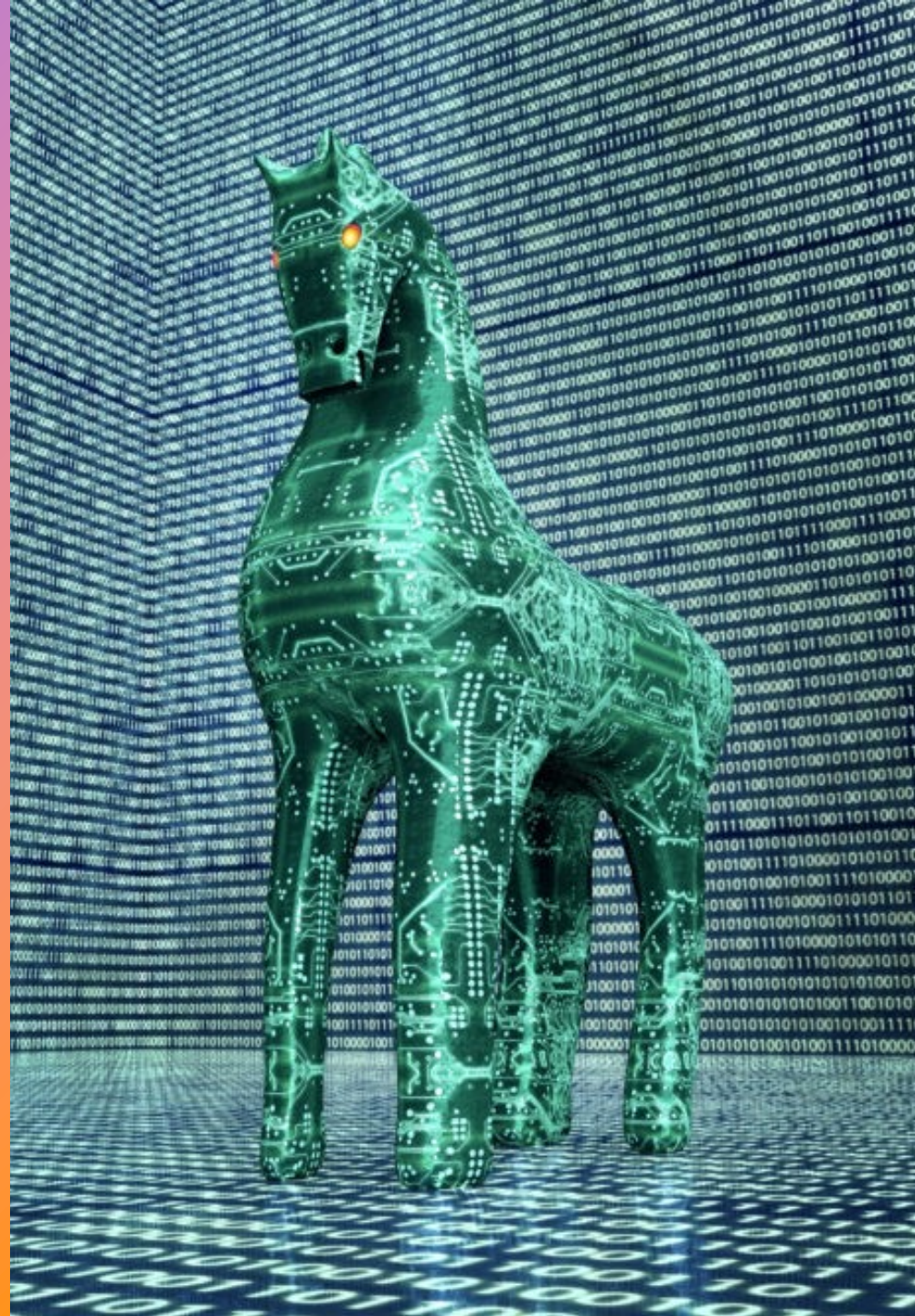
Furin is a protease, a proteolytic enzyme that in humans and other animals is encoded by the *FURIN* gene. Some proteins are inactive when they are first synthesized, and must have sections removed in order to become active. Furin cleaves these sections and activates the proteins.[5][6][7][8] It was named furin because it was in the upstream region of an oncogene known as FES. The gene was known as FUR (FES Upstream Region) and therefore the protein was named furin. Furin is also known as **PACE** (Paired basic Amino acid Cleaving Enzyme). A member of family S8, furin is a subtilisin-like peptidase.

FCoV replication cycle and sites for S activation



FCoV replication cycle and sites for S activation. Replication cycle starts with viral binding to the cellular receptor. The virus is endocyted and viral-cell fusion allows the delivery of the (+) genomic RNA (gRNA) to the cytoplasm, to initiate the genome replication and the protein synthesis. Sub-genomic RNAs (sgRNAs) are transcribed and translated. Structural proteins S, E and M are folded and post-translationally modified at the ER. Viral assembly takes place in the ERGIC and viruses are released through exocytosis. Activation of S proteins (scissors) can take place at: **1.** The cell membrane during viral attachment (S1/S2 site); **2.** The endosome to induce viral-cell fusion (S2' site); **3.** The trans-Golgi network during viral assembly (S1/S2 site); **4.** The secretory vesicle during viral egress (S1/S2 site); and **5.** The cell membrane during viral release (S1/S2 site). Adapted from: Millet and Whittaker (2015).

HIJACKED MACROPHAGES MONOCYTES AND TROJAN HORSES



STEALTH

- The FIP virus-laden macrophages and monocytes escape detection from host immune system
- There is an absence of surface expression of FIPV antigens on infected cells isolated from cats with FIP
- Invitro studies show that the surface antigens on the macrophages are internalized after addition of antibodies. This leaves the cell membranes cleared of visually detectable viral antigens
- This absence of surface antigens allows the now hijacked macrophages and monocytes to escape detection
- These cells transporting the virus escape antibody-dependent cell lysis
- There is further signaling from the macrophages which destroy T-Lymphocytes

ROLE OF MACROPHAGES AND MONOCYTES IN FIP

- Allow attachment of FIPV
- Allow entry of FIPV
- Allow replication of FIPV
- Transport FIPV
- Apoptosis of Tcells due to signaling mediators from infected macrophages

AAFP/EveryCatFelineInfectiousPeritonitis DiagnosisGuidelines (2022)

Immunological response

Monocytes'/macrophages' main functions within the immune system include phagocytosis of foreign material,
antigen presentation and cytokine production. Monocytes/macrophages usually respond to FCoV infection by presenting viral antigens on their surface, leading to antibody-dependent, complement-mediated lysis and cell
death (5,28,29); however, FIP immune system evasion can occur whereby some FIP-infected macrophages lack
surface expression of viral antigens, thus allowing the infected macrophages to persist (28). Once infected by FCoV, macrophages become activated leading to the production of a variety of inflammatory mediators (30). These cytokines include IL-1β, IL-6, IL-15, TNF-α, the interferons α, β, and γ, and the chemokines CXCL10 and CCL8 (see supplemental 5b) (30). In addition, upregulation of macrophage adhesion molecules leads to interaction with the endothelial cells of smaller veins (30,31). The expression of enzymes, such as matrix metalloproteinase 9, is also increased (32). Compromise to the endothelial barrier leads to vasculitis, perivascular necrosis and monocyte extravasation. Leukocytes that remain uninfected, such as neutrophils, also
become activated and likely contribute to endothelial cell damage. Increased expression of vascular endothelial
growth factor by activated macrophages is also believed to enhance vascular permeability (33)

FORMS OF FIP DISEASE

WET or Effusive FIP:
A pyogranulomatous condition of the omentum, and serosal surfaces of affected organs. This leads to effusions in the thorax and/or abdomen

Dry FIP:
A granulomatous organ inflammation affecting kidneys, pancreas, lymphnodes and the CNS

Both forms can develop ocular and CNS disease

The clinical signs of FIP are variable and depend on the affected organs and may include fever, jaundice, effusion, weight loss or neurological signs and ocular lesions (Pedersen, 2014).

WET FIP

DRY FIP

NEUROLOGICAL FIP

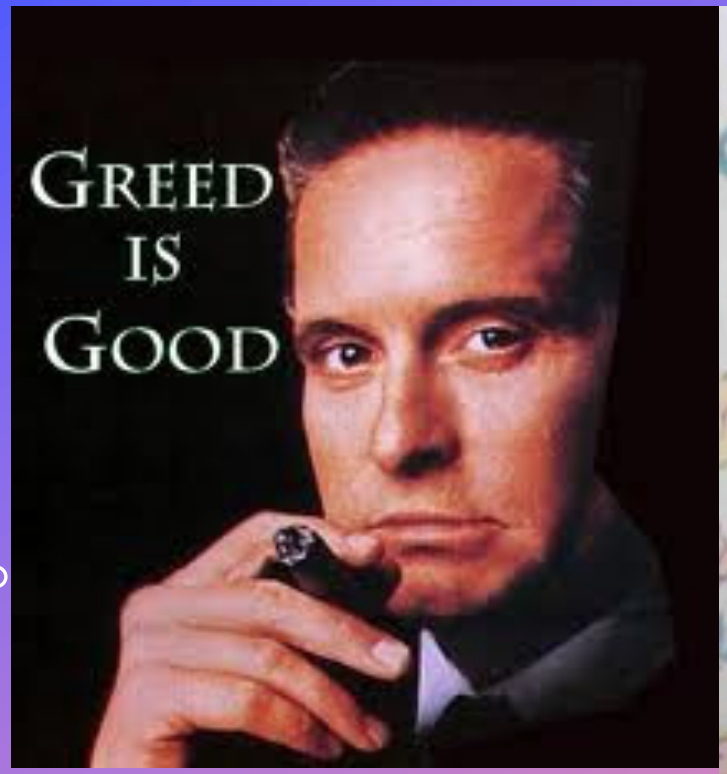
PATIENT AGE

TRANSMISSION OF FIP ?

- Feline enteric Coronavirus (FeCoV) can cause an asymptomatic infection or one with mild gastrointestinal signs
- FeCoV is highly contagious and is transmitted by the fecal-oral route. 80-90% of cats are infected
- FIP virus has been shown by Pederson to be present in the feces of experimentally infected cats, but the virus was not infectious when tested via the oral-nasal route

DISEASE OUTCOMES: HISTORICAL, CURRENT

VIRAL MUTANT MANTRA



R790S

R793S

R790G

INTERNAL CLIMATE CRISIS


THE FLOOD:
WET FIP

SYSTEMIC INFLAMMATION

- Clinicopathological features include fever, vasculitis, and serositis, with or without effusions
- There is increased cytokine release
- **Hepatocytes and cardiomyocytes are a source of inflammatory cytokines in FIP**
- Cytokine expression was mainly evident in the bile duct epithelium
- Transcription of IL-1β, IL-6, IL-10, IL-12, and TNF-α was significantly upregulated in the liver of FIP cats
- In cardiomyocytes the pyrogenic cytokines IL-6 and TNF-α were upregulated in FIP
- IL-1β, IL-6, and TNF-α are the major inflammatory cytokines in cats
- IL-1β and TNF-α may also contribute decreased albumin production, and increased muscle breakdown and weight loss seen in FIP
- IL-6 is significantly higher in the effusive form compared to the dry form
- IL-6 can induce vascular endothelial growth factor (VEGF) production and pulmonary vascular permeability
- **The degree of ascites was found to be correlated with serum VEGF levels in cats with FIP**

CLINICAL SIGNS OF WET/EFFUSIVE FIP

- The most severe and acute for of FIP
- Ascites
- Abdominal mass effect due to adhesions
- Dyspnea, muffled heart sounds, cyanosis secondary to pleural effusions
- Pericardial effusion
- Lymphadenopathy
- Generalized synovitis and lameness
- Scrotal enlargement

These are of course in addition to the nonspecific signs of anorexia lethargy pyrexia vomiting diarrhea jaundice

WET FIP

- The typical fluid from a cat with FIP is viscous, straw-colored, clear to moderately cloudy and usually forms clots or strings due to its high protein content
- The fluid appears as ascites and or pleural effusion
- Elevated gamma globulins
- Due to low albumin and high globulin concentration A:G ratio < 0.6
- 2/3 of cats with FIP present with the wet form

DESERTIFICATION: DRY FIP

CLINICAL SIGNS OF DRY FIP

- Ocular lesions:
- Anterior uveitis
- Change in Iris color
- Retinal hemorrhage
- Retinal detachment
- Blindness
- Neurologic lesions:
- Ataxia
- Seizures
- Paresis
- Cranial nerve deficits
- Behavior changes
- Gastrointestinal lesions:
- Vomiting
- Constipation
- Diarrhea
- Thickened bowel loops

These are of course in addition to the nonspecific signs of anorexia lethargy pyrexia vomiting diarrhea jaundice

SIGNS OF DRY FIP

- Organ granulomas
- Abdominal
- Thoracic
- Eyes
- Brain
- Neurological or Ocular disease occurs in 70% of Dry FIP cases

THE BLOOD EYE / BRAIN BARRIER

- The efficiency of the barrier decreases decreases in inflammatory states
- The virus can cross the inflamed barrier
- The efficiency increases as inflammation subsides
- The virus therefore becomes shielded by the reestablished barrier
- Increasing blood levels are needed to enable drugs to cross the barrier
- Signs of neurological/ocular disease occurs after systemic signs subside
- CNS inflammation does not cause significant changes in hematology
- CSF IgG anti coronavirus antibody titers of 1:640 or greater only found in cats with FIP

NEUROLOGICAL & OCULAR FIP

- More common in Dry than Wet FIP
- Can be seen prior and post antiviral therapy
- Retarded growth in kittens
- Unilateral or bilateral anterior uveitis
- Retinitis
- Retinal hemorrhage
- Dementia
- Aggression
- Seizures
- Ataxia
- Incontinence
- Tail and hindleg paralysis

HISTORICAL OUTCOMES

- Natural death or euthanasia was several days to weeks after initial diagnosis
- The greatest survival (approx. 1 year) was in mild cases of dry FIP with symptomatic care

HEMATOLOGY

BIOCHEMISTRY

HISTOPATHOLOGY

DIAGNOSTIC TESTING

- Rivalta Test
- The Gold Standard: Staining the viral antigen in macrophages, which are surrounded by pyogranulomatous lesions, by means of histopathology or immunohistochemistry
- Real time PCR on fluids from body cavity effusions
- FECV is no longer excreted in the feces due to the mutation of the virus, therefore FCoV PCR from fecal samples is of little help in making a diagnosis
- In most effusions associated with FIP , the A:G ratio is < 0.9

RIVALTA TEST

- The Rivalta test principle relies on the formation of a precipitate when an effusion is added to acetic acid.
- This helps differentiate whether a fluid is an exudate or a transudate. Exudates have a higher concentration of proteins than transudates.
- Low concentrations of proteins dissolve in the acetic acid solution
- High concentrations of proteins do not dissolve in the acetic acid solution

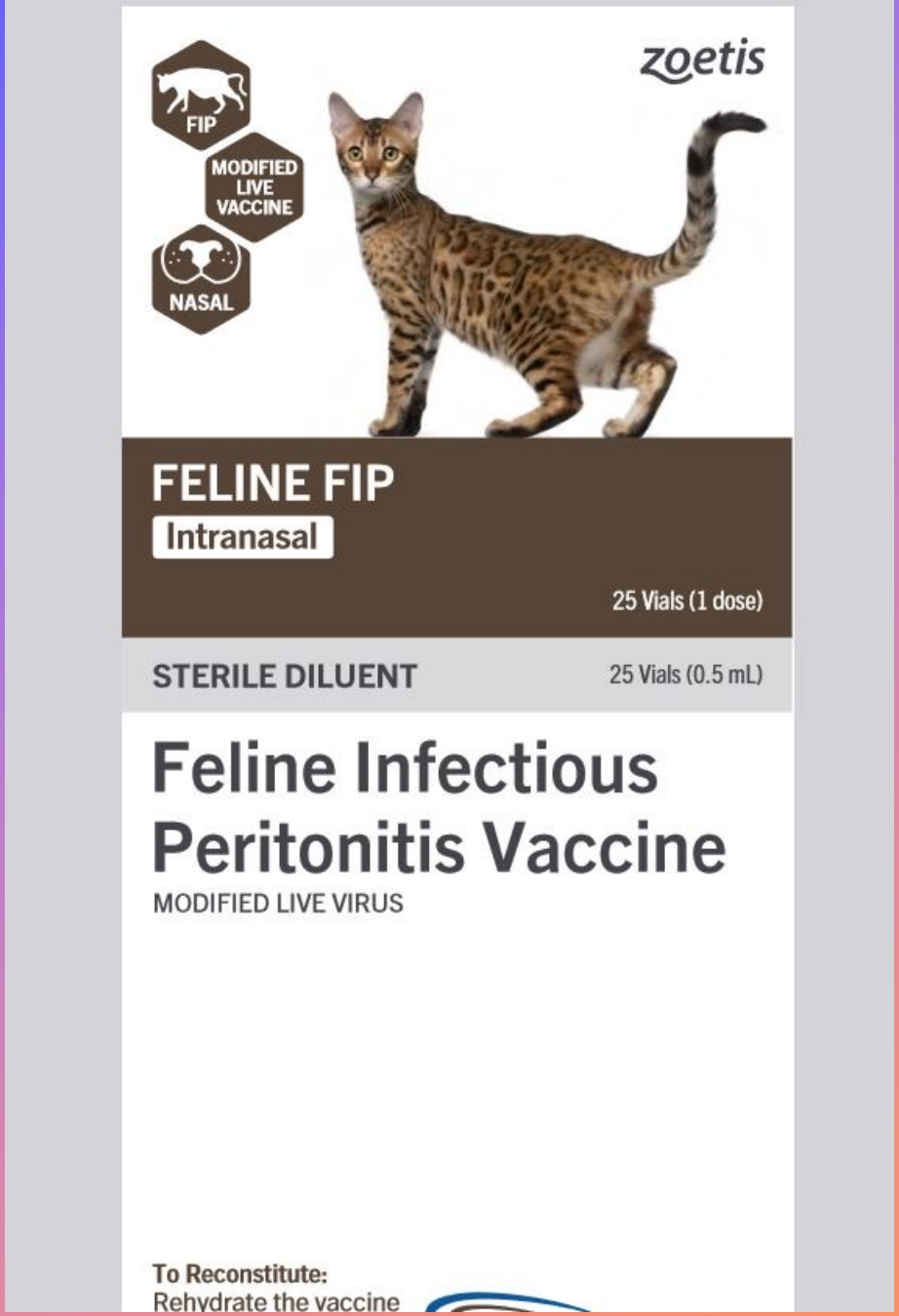
RIVALTA TEST PROCEDURE

The test distinguishes between a transudate and an exudate

- Place 8 ml distilled water in a 10 ml reagent tube
- Add 1 drop of acetic acid
- Mix thoroughly
- Carefully add 1 drop of the effusion without mixing
- Hold against a dark background and observe
- Negative if drop of effusion dissolves leaving clear reagent
- Positive if drop beads and either floats on the surface or sinks

DISEASE PREVENTION: VACCINES? HUSBANDRY?

YES ?


zoetis
FIP
MODIFIED LIVE VACCINE
NASAL
FELINE FIP
Intranasal
25 Vials (1 dose)
STERILE DILUENT
25 Vials (0.5 mL)
Feline Infectious Peritonitis Vaccine
MODIFIED LIVE VIRUS
To Reconstitute:
Rehydrate the vaccine

NO ?

FIP VACCINE

- AAFP None Core Vaccine
- Intranasal vaccine
- Two administrations 3 weeks apart for initial vaccination
- Unlikely to be effective in cats previously exposed to coronavirus
- Cats are commonly exposed to coronavirus before they can be vaccinated

FIP VACCINE ANTIBODY DEPENDENT ENHANCEMENT (ADE)

Antibody attaches to the virus
The virus is taken in by the macrophages

HUSBANDRY

ROLE OF PROTEASES IN VIRAL REPLICATION A FAMILY AFFAIR

- Many viruses encode proteases to enable and to sustain replication.
- The viral genome encodes a polyprotein with an embedded viral protease that cleaves the polyprotein at several specific sites to generate mature viral proteins.
- Viral proteases are therefore ideal therapeutic targets.
- The cleavage sites recognized by a given viral protease are generally diverse in amino acid sequence and processed at different rates, to produce infectious virus.
- This ability to specifically recognize and cleave diverse substrate sequences is conserved for proteases of different families of viruses.
- The protease inhibitor GS-376 is used in the treatment of Feline Infectious Peritonitis

NUCLEOSIDE ANALOGS

- Nucleoside analogs contain a nucleic acid analog and a sugar
- These analogs act as alternate substrates and RNA-chain terminators of viral RNA dependent RNA polymerase.
- Become incorporated into viral genomes and cause disruption of viral replication
- The nucleoside analog **GS-441524** strongly inhibits feline infectious peritonitis (FIP) virus in tissue culture and experimental cat infection studies

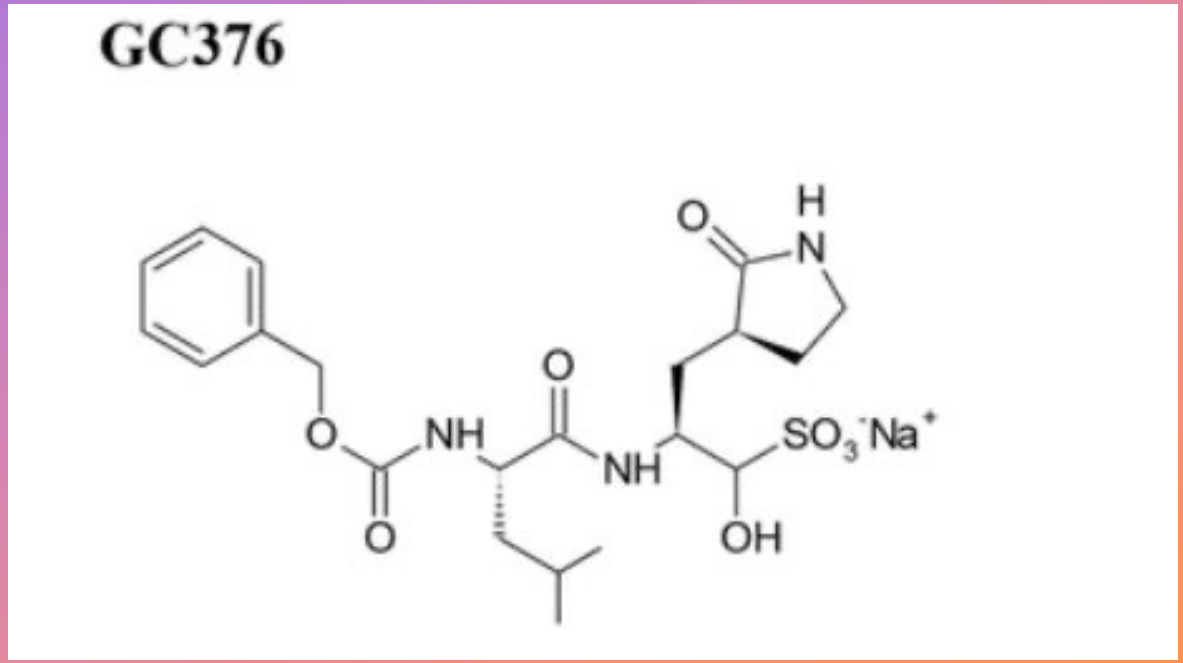
CURRENT “LEGAL” THERAPIES

- Prednisolone
- Pentoxyfylline
- Prayer
- Fluids
- Antibiotics
- Fluid therapy
- Pain meds
- Appetite stimulants
- Repeat

CURRENTLY AVAILABLE TREATMENTS

- Protease inhibitors
- Nucleoside analogs

PROTEASE INHIBITOR GC376



PROTEASE INHIBITOR GC376

- GC376 a 3C-like protease ($3CL^{pro}$) inhibitor, targets the viral 3CL protease
- Small molecules with easy entry into cells
- Terminate viral RNA transcription
- GC376 is administered S/Q q 12h
- GC376 slowed the development of permanent teeth in young kittens, and caused hair loss
- Protease inhibitors are less efficient in crossing the blood brain barrier than the nucleoside analogs

NUCLEOSIDE ANALOG GS-441524

- Nucleoside analog (GS –441524)
- Small molecules with easy entry into cells
- GS : More efficaceous than GC
- Terminate viral RNA transcription
- The nucleotide analog remdesivir (RDV), is a phosphoramidate prodrug of GS-441524
- Neurological and ocular disease have a decreased response to either medication

DEVELOPING RESISTANCE TO GC376

- Although remarkable results have been achieved, it has been found that long-term use of GC376 in cats may lead to weakening of the effect or recurrence after cure.
- Studies have shown that long-term use of viral protease inhibitors results in the development of inhibitor-resistant viral mutants, which may contribute to the development of disease

| Veterinary Microbiology | Research Article | 24 August 2022

Adaptive Mutation in the Main Protease Cleavage Site of Feline Coronavirus Renders the Virus More Resistant to Main Protease Inhibitors

Authors: Zhe Jiao, Yuanyuan Yan, Yixi Chen, Gang Wang, Xiaowei Wang, Lisha Li, Mengfang Yang, Xiaoshuai Hu, Yilin Guo, Yuejun Shi, Guiqing Peng | AUTHORS INFO & AFFILIATIONS

DOI: https://doi.org/10.1128/jvi.00907-22 • Check for updates

ABSTRACT

The rapid global emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused serious health problems, highlighting the urgent need for antiviral drugs. The viral main protease (M^{pro}) plays an important role in viral replication and thus remains the target of choice for the prevention or treatment of several viral diseases due to high sequence and structural conservation. Prolonged use of viral protease inhibitors can lead to the development of mutants resistant to those inhibitors and to many of the available antiviral drugs. Here, we used feline infectious peritonitis virus (FIPV) as a model to investigate its development of resistance under

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The nucleoside analog GS-441524 strongly inhibits feline infectious peritonitis (FIP) virus in tissue culture and experimental cat infection studies

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Affiliations + expand

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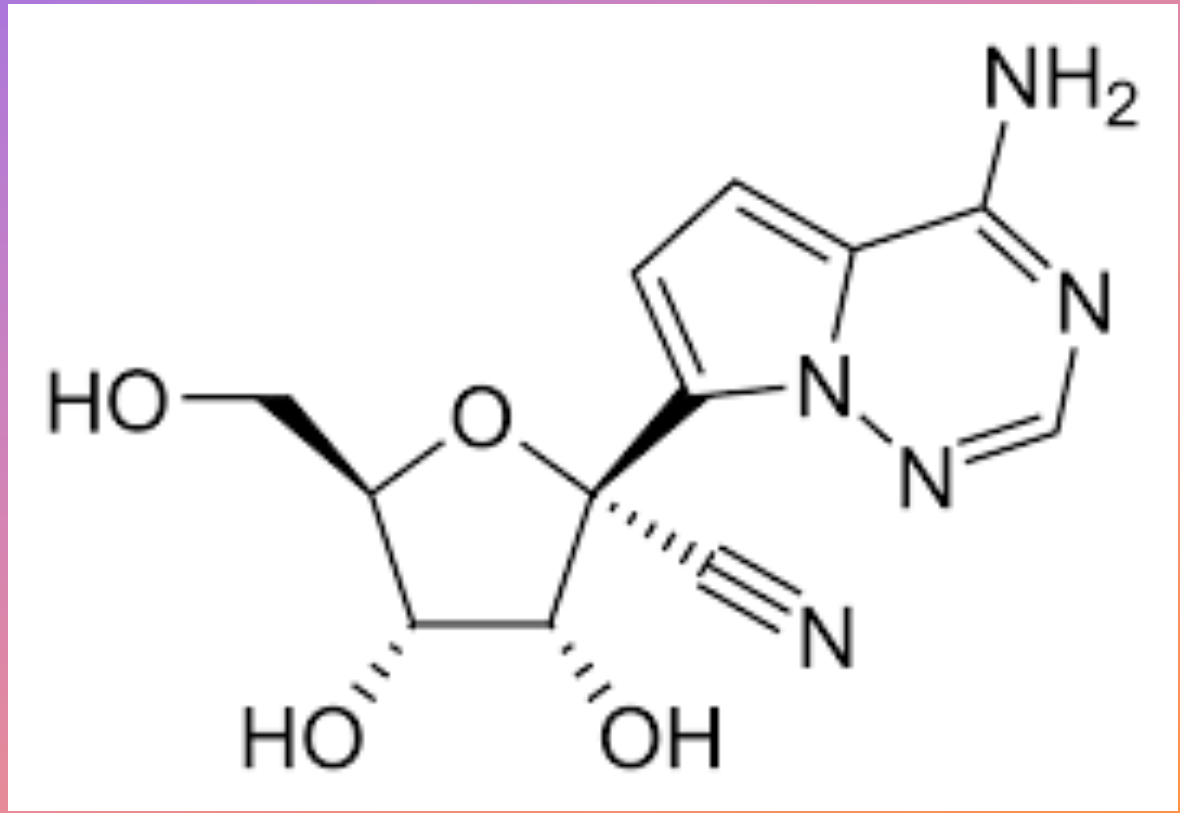
Abstract

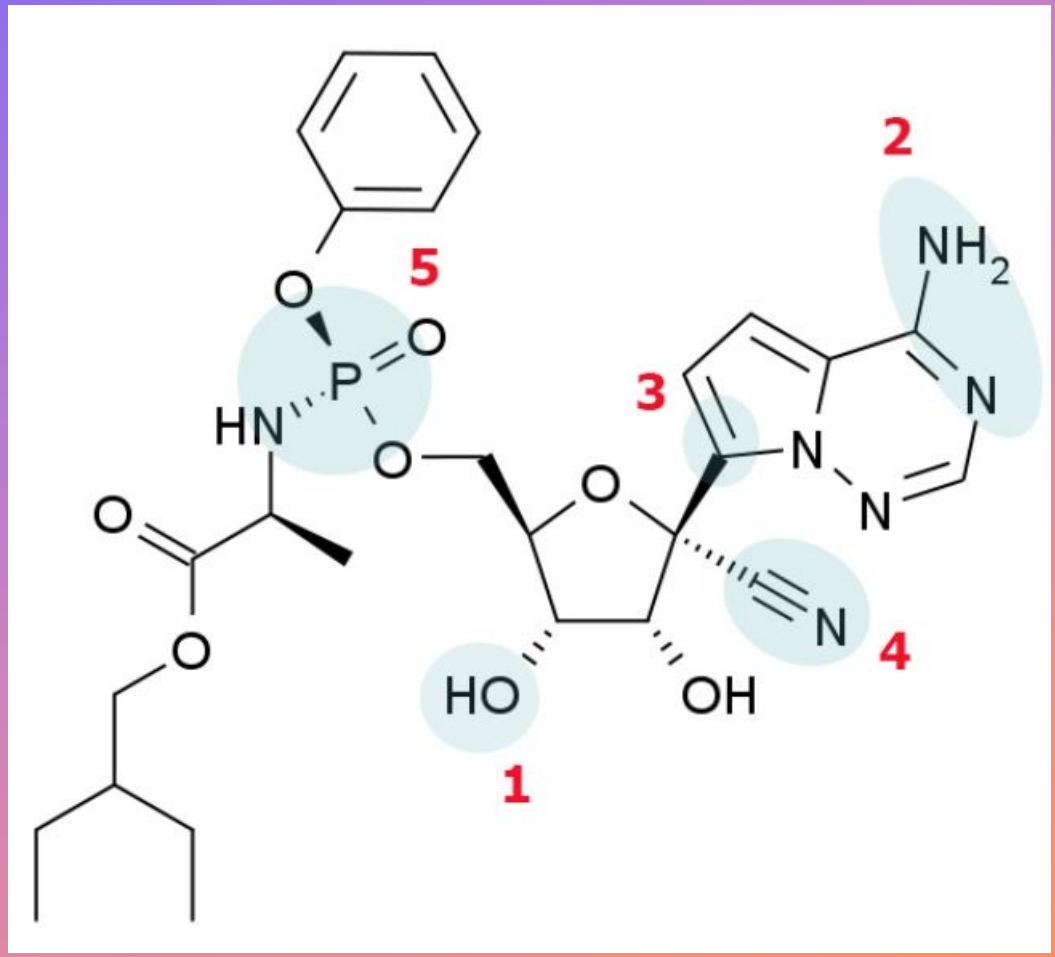
Feline infectious peritonitis (FIP) is a common and highly lethal coronavirus disease of domestic cats. Recent studies of diseases caused by several RNA viruses in people and other species indicate that

STRUCTURE OF GS-441524



REMDESIVIR

A prodrug for GS-441524



MOLNUPIRAVIR (EIDD-2801)

- Closely resembles GS-441524
- Used in cats with resistance or relapse from GS-441524 treatment
- Oral medication
- Recommended for neurological or ocular FIP
- 8-10 mg/kg po q 12 h for 84 days

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PEDERSEN'S TREATMENT PROTOCOL FOR FIP USING INJECTABLE GS-441524

- The starting dosage for cats with wet or dry FIP and no ocular or neurological disease signs is 4-6mg/kg daily for 12 weeks, with the younger and wet cases tending to go toward the lower end, and the dry cases toward the higher end.
- Cats with ocular lesions and no neurological signs start at 8 mg/kg daily for 12 weeks.
- Cats with neurological signs start at 10 mg/kg, daily for 12 weeks.
- If cats with wet or dry FIP at the beginning develop ocular or neurological signs they go to the appropriate ocular or neurological dosage.
- There is an oral form of GS available from at least two sources out of China (Aura, Mutian) not recommend it when the injectable dosage goes above 10 mg/kg daily,as the efficiency of oral absorption goes down at these high dosages.
- Treat relapses at dose 5mg/kg higher than previous treatment dose for 8 weeks.

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RECOVERY

Abstract

Feline infectious peritonitis (FIP) is a common and highly lethal coronavirus disease of domestic cats. Recent studies of diseases caused by several RNA viruses in people and other species indicate that antiviral therapy may be effective against FIP in cats. The small molecule nucleoside analog GS-441524 is a molecular precursor to a pharmacologically active nucleoside triphosphate molecule. These analogs act as an alternative substrate and RNA-chain terminator of viral RNA dependent RNA polymerase. We determined that GS-441524 was non-toxic in feline cells at concentrations as high as 100 uM and effectively inhibited FIPV replication in cultured CRFK cells and in naturally infected feline peritoneal macrophages at concentrations as low as 1 uM. We determined the pharmacokinetics of GS-441524 in cats in vivo and established a dosage that would sustain effective blood levels for 24 h. In an experimental FIPV infection of cats, GS-441524 treatment caused a rapid reversal of disease signs and return to normality with as little as two weeks of treatment in 10/10 cats and with no apparent toxicity.

Keywords: Cell culture; EC50; Experimental infection; FIP virus (FIPV); Feline infectious peritonitis (FI

FIP Gs-441524 Treatments

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1

ed over 12,000 cats to cure FIP in USA and Canada. We're the only one that offers "Lifetime Cure & No Relapse and
oin our FIP Warriors Facebook group and save your little fur life with us now!

Check Our Lifetime Cure&No Relapse Guarantee Policy

COMBINATION OF PROTEASE INHIBITOR AND NUCLEOSIDE ANALOG THERAPY

- GS-441524 combined with GC376 can be safely and effectively used to treat FIP
- Combination treatment period is reduced to 4 weeks
- Excellent cure rate
- Important to weigh the patient every 2 weeks for accurate dosing
- In one study 45 of 46 cats survived
- No relapses were observed after 10 months

WHAT DOES THE FUTURE HOLD?

THANK YOU!

- B. Anthony Nanton BSc DVM DABVP (Feline)