

2023 report on the status of SOCK FIP and FIP research at UC Davis and possible directions for future FIP research

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We hoped that 2023 would see legalization of one or more antiviral drug for cats. With the exception of a few countries outside of the USA, this is not the case. Nonetheless, there is hope that studies being done at UC Davis and elsewhere in the world will help promote conditionally and/or fully approved human drugs, such as Remdesivir, Molnupiravir, and Paxlovid, to be used by veterinarians. Even if approved for animal use, drugs marketed for humans are not ideal, because they must be purchased at the price set for humans. Therefore, the unapproved market will remain a major source for cheaper antivirals for many years to come. However, SOCK FIP appreciates the efforts of countless cat owners and to pressure industry and governmental agencies to allow for the use of effective antiviral drugs for cats. These efforts have seen varying degrees of success in a number of countries outside of the US.

FIP research at UC Davis in 2023 and supported by donations to SOCK FIP

2023 has seen continuing support for SOCK FIP and feline coronavirus research at UC Davis and we could not have done this without the help of numerous donors. Two current research projects receiving funds from SOCK FIP are of particular interest. The first project involves antiviral drug trials and is led by Drs. Krystle Regan and Brian Murphy. Patients and owners were recruited from around the USA. In the first trial, two antiviral drugs were compared head-to-head in cats with wet FIP to compare the cure rates with either oral GS-441524 or Remdesivir (Gilead). This trial, which has now been published, demonstrated that oral Remdesivir works as well as oral GS-441524. Therefore, if Remdesivir achieves full approval in the United States, veterinarians can feel comfortable prescribing it for cats with wet FIP. Additional studies comparing GS-441524 and Remdesivir in cats with dry FIP, and Molnupiravir (Merck) in cats with wet FIP, have also been completed. The results of these studies should be published early in 2024. A final trial involving Paxlovid (Pfizer). Paxlovid has recently become fully approved and widely available in the United States, and if it proves safe and effective in cats with FIP, it would be a third human antiviral drug treatment for FIP that may be someday used by veterinarians. Drs. Regan and Murphy also utilized their field trial cases to study the cause for deaths during the first two weeks of treatment. This population represents up to 10% of treated cases around the world. Necropsies demonstrated the existence of serious complicating diseases that often involved bacterial sepsis, frequently with highly antibiotic resistant organisms, as well as serious disease of the heart. Further work is needed to determine the nature of heart disease and how much might be pre-existing and how much is caused by the FIP virus.

A second major research project on FIP prevention is being undertaken by Dr. Patricia Pesavento, one of our veterinary pathologists, and her research team that includes veterinary microbiologist Terza Brostoff, biomedical engineer Randy Carney, immunologist Dennis Hartigan O'Connor, and laboratory technician Ken Jackson. Their study involves the development of an

mRNA vaccine against a part of the nucleocapsid protein that is shared by virtually all known feline coronavirus isolates. The theory is that an immune response to this protein, as compared to the commonly used spike protein in COVID-19 vaccines, will protect against development of FIP in cats exposed to the common enteric form of feline coronavirus. This would be analogous to the protection against severe and chronic forms of COVID-19 being reported for mRNA vaccines. Dr. Pesavento's team have constructed a vaccine based on ideal production parameters and have tested it for both safety and efficacy in a rodent model. Development of this mRNA vaccine will only be a first step, as it will need to be further tested in a limited number of cats as a prelude for much larger scale field testing in larger populations of cats, such as catteries or foster/rescues, that are experiencing on-going FIP cases.

Areas for future FIP research

The discovery of a cure for FIP does not end the need for further FIP research. Hopefully, veterinary scientists around the world who are still active in academia and industry will consider some of the following fertile areas of study. Such studies involve every aspect of FIP pathogenesis, from the underlying enteric coronavirus that is enzootic in virtually all healthy cat populations and exist in the lower intestinal tract, to mutant forms that have acquired an ability to infect monocyte/macrophages within and outside of the abdomen. The exact nature of immunity to feline coronaviruses, both the minimally pathogenic enteric form, and the highly lethal FIP causing form, needs to be elucidated. We know that immunity to both intestinal and extra-intestinal forms of the virus is tenuous, short-lived, and susceptible to weakening by internal and external stressors. Immunity to enteric coronavirus appears to involve locally produced antibodies, while immunity to mutant FIP-causing viruses involves a more systemic lymphocyte-mediated (cellular) immune responses. Exact knowledge of the strengths and weaknesses of both types of immunity will be essential for all future vaccine development efforts. Do you prevent FIP by attacking the underlying enteric coronavirus infections or by attacking FIP-causing mutants as they occur?

There is a critical need to develop tests that can accurately predict when a cat has been cured by antiviral drug treatment. We know that some cats can be cured in as little as 4-6 weeks, while some take up to 12 weeks. We suggest treating for 12 weeks because this yields the maximum cure rate, but in so doing, we know that some cats will be over-treated. The only current manner to determine when a cat is cured is by withdrawing treatment and seeing whether the disease relapses. Periodic complete blood counts and a basic serum chemistry panel are helpful when coupled with outward measures of physical health in monitoring and managing a treatment, but a return to normal test values and outward health do not assure against a post-treatment relapse. Conversely, the persistence of minor abnormalities in blood and health are not always signs that a cure has not occurred and that a dosage needs to be increased or treatment extended. This has been especially true for cats with neurological FIP, where blood test results and status of neurological deficits are not always predictive of a cure.

Although there is hope that even more effective anti-viral drugs will be found in the future, the well documented safety and efficacy profiles of current drugs leave very little room for further

improvement. However, evolving drug resistance is now recognized in some cats. We should apply what is known about how drug resistance evolves in chronic infections such as HIV/AIDS to FIP. The most effective way to combat drug resistance in HIV/AIDS is to combine two or more antiviral drugs with different modes of action before resistance develops.

It appears that some feline coronavirus strains may be more neurotropic than others. The predilection for infecting the central nervous system may evolve specific mutations in the enteric coronavirus strains that are enzootic in the environment, or mutations that occur as part of the FIP biotype. The role of the blood-to-brain barrier, and the apparent compartmentalization of immunity between the central nervous system and the rest of the body are additional areas requiring study.

Most cat owners are now aware of the large outbreak of FIP that is occurring in the island of Cyprus. It is still uncertain whether this outbreak qualifies as an epizootic (epidemic) or an enzootic (endemic). Preliminary research suggests that the outbreak is associated with closely related serotype 2 (canine coronavirus-like) isolates of FIP virus. Whether this outbreak is associated with cat-to-cat spread (i.e., epizootic disease) or disease enhancing factors in the environment (i.e., enzootic disease) is of obvious importance for cats in all parts of the world. The worse possible scenario is to see a COVID-19 type pan-epizootic. Hopefully, researchers in Cyprus, the UK and elsewhere will be able to solve the nature of this outbreak as quickly as possible.