FELINE INFECTIOUS PERITONITIS
New Antiviral Drugs Help Fight Fatal Disease
“Luna,” a 2-year-old female higher-generation Savannah, is a feline infectious peritonitis (FIP) survivor, thanks to taking part in a clinical trial to determine the effectiveness of an antiviral drug in helping cats with the highly fatal disease.

When Debra Roberts of Westerville, Ohio, brought Luna home at 10 weeks of age, the kitten was playful, energetic and loving. At about 13 ½ weeks old, Luna was vaccinated for feline distemper. “A few days later, my husband, Jamison, noticed her belly was swollen. He called me at work to come home, because she had become increasingly lethargic. We took her to an emergency clinic,” Roberts says.

Luna also had lost her appetite and was running a fever. The emergency veterinarian diagnosed Luna with the wet or effusive form of FIP and gave the kitten less than
two weeks to live. Roberts, a nurse for 28 years at a large teaching hospital, began looking for a clinical trial for FIP. She found a trial underway at the University of California-Davis. “We were in the right place at the right time,” she says.

“We traveled to California when Luna was 14 ½ weeks old, so she could be treated. Right away, after the first injection, her appetite and fever improved, and soon her lab tests were normal. After six days, she was released to continue the treatment at home.”

After 12 weeks of daily injections, which were completed in July 2017, Luna’s FIP went into remission. Today, the beautiful spotted feline continues to be healthy, active and free of signs of the disease.

“We don’t really know if Luna is in remission or cured, but she’s a poster child for FIP research,” Roberts says.

FIP VIRUS REPLICATION

Feline infectious peritonitis (FIP) is the cause of death of 0.3 to 1.3 percent of all cats seen at veterinary institutions around the world, and the most important viral disease of cats under 3 years of age. FIP is especially common among kittens and cats from shelters, rescues and pedigree catteries.

The clinical trial at the University of California-Davis in which Luna participated was to evaluate the effectiveness of a new antiviral drug, GS-441524, against FIP. It is the second antiviral drug to be tested at the university. The results of this trial are soon to be published in the *Journal of Feline Medicine and Surgery*.

Thirty-one cats ranging from 3 months to 6 years of age were enrolled in the trial, including 26 cats presenting with the wet or effusive form of FIP and five cats had the dry or non-effusive form of FIP. Five cats died soon after admission, because of severe disease and complications, and 26 cat quickly returned to normal health and completed the 12-week primary treatment course.

Eighteen of these 26 cats remained healthy, and eight others suffered disease relapses within one to 12 weeks that required additional treatments, often at a higher dosage. Ultimately 25 of the 26 cats that were treated for 12 weeks or longer achieved full remission. One of these cats subsequently died of unrelated congenital heart disease, but the 24 remaining cats are still healthy after periods as long as 18 months. Luna was the first cat to complete treatment in this trial.
“We have treated cats with GS-441524 that have been out of treatment for over a year and a half and are still healthy,” says lead investigator Niels Pedersen, DVM, PhD, distinguished professor emeritus and retired director of the Center for Companion Animal Health. “We believe it is a safe and highly effective treatment for FIP.”

An earlier antiviral drug, GC376, was shown to be successful in a clinical trial also conducted at the University of California-Davis. GC376 was developed by Kansas State University virologists, Yunjeong Kim, DVM, PhD, DACVIM, associate professor of diagnostic medicine and pathobiology, and Kyeong-Ok Chang, DVM, PhD, professor of diagnostic medicine and pathology.

“GC376 and GS-441524 both inhibit the replication of the FIP virus, but by two different mechanisms,” explains Dr. Pedersen.

When the FIP virus invades a normal cell, it releases a strand of its RNA into the host cell that is reproduced and converted into the microRNAs that direct the synthesis of different viral proteins. The original RNA strand is copied by assembling its four nucleotides — guanine, uracil, adenine and cytosine — into a new RNA chain. The order of the four nucleotides defines the genetic instructions each chain transmits for the creation of a specific protein.

“GS-441524 is an adenosine nucleoside analog, which means it is a nucleotide precursor,” Dr. Pedersen says. “It mimics a normal nucleoside, though it differs a small but critical degree. Cells will take up GS-441524 like a normal adenosine nucleoside and use it to form what would normally be an adenine nucleotide. That nucleotide then becomes one of the parts of the growing RNA chain, except the adenine part of this nucleotide is defective. Thus, the nucleotide with GS-441524 blocks the next nucleotide from joining and permanently terminates the whole chain, preventing it from creating the viral protein.”

In comparison, GC376 targets 3C-like (3CL) protease, an enzyme that acts like scissors to cut out single proteins from a large sheet of connected proteins. “A coronavirus
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produces long polyproteins where individual proteins are clumped together,” Dr. Kim explains. “These long polyproteins should be clipped apart by viral proteases, liberating individual proteins that can start virus replication. Protease inhibitors like GC376 bind to and inhibit this process, so no progeny viruses are produced.”

GC376 and similar 3CL proteases showed promise in earlier studies of coronaviruses and calciciviruses, two important RNA viruses in cats. In collaboration with Dr. Pederson’s research team, the Kansas State researchers cured six young cats with otherwise fatal FIP by treating them with GC376 for two to three weeks. The results of that study were published in March 2016 in the journal PLOS Pathogens.

“Our results provide the first evidence that a direct-acting antiviral agent is effective at reversing the immune-mediated disease progression caused by coronavirus infection, even when the antiviral treatment was started at clinically advanced stages,” says Dr. Kim.

A subsequent clinical trial was conducted in 2016, once again in collaboration with the University of California-Davis researchers. This study of 20 cats from 3 months to nearly 7 years of age evaluated the effectiveness of GC376 in treating cats with various forms and stages of FIP. This study showed that up to 12 weeks of

WHEN A CAT HAS FELINE INFECTIOUS PERITONITIS VIRUS

Feline infectious peritonitis (FIP) is caused by a mutant form of a highly contagious but common virus that lives in a cat’s intestinal tract, feline enteric coronavirus (FECV). FECV causes mild illness in 80 to 90 percent of infected cats but is highly infectious and can be shed by cats for long periods through feces.

Although FECV spreads rampantly in multiple-cat households, most cats with FECV do not become ill. Rarely, does FECV mutate into FIP. Although FECV is highly contagious, the FIP virus is not. The mutation that causes FIP is believed to occur in individual cats that cannot fight off the new type of infection. It is estimated that 20 percent of cats may have natural immunity due to complex, interacting genetic factors.

FIP commonly affects kittens and cats with weak immune systems, thus it is a leading cause of death in cats under 3 years of age. When a cat has FIP, the mutant virus invades and hijacks host cells of the immune system — macrophages in tissues and white blood cells called monocytes. This spreads the disease causing inflammatory reactions.

There are two types of FIP: the wet or effusive form and the dry or non-effusive form. Experts say that infected cats may switch or show both forms of FIP. The wet form is diagnosed more often, and it progresses faster, as fluid accumulates in the abdomen and chest. The dry form develops slower, is harder to recognize and can cause inflammatory lesions on organs including the brain.

Treatment for cats diagnosed with FIP traditionally has been limited to supportive care with corticosteroids, antibiotics and fluid therapy. Preventive practices in catteries and multicat households include good husbandry; separating kittens from adult cats; selective breeding that includes not breeding cats, especially male cats, that have produced FIP-susceptible offspring and reducing inbreeding; reducing the number of breeding animals to no more than six cats; and maintaining smaller populations of cats and kittens.
treatment was required to achieve permanent disease remission and that disease relapses were a problem if treatment was stopped too soon and/or if neurological involvement occurred. Ultimately, seven of the 20 cats in the trial remained in remission after the treatments ended and six cats are still healthy today, over three years later. An article of the clinical trial was published in September 2017 in the Journal of Feline Medicine and Surgery.

Because eight cats in this study developed neurological disease and died, the researchers suspect that FIP spreads to the brain in advanced stages of the disease. Treatment with higher doses of GC376 slowed but did not improve the neurological signs, indicating the challenge of getting the drug to cross the blood-brain barrier.

**FIP PREVENTION IS A GOAL**
The advances in being able to successfully treat some cats with FIP with the GS-441524 and GC376 antiviral drugs could not have been imagined only a few years ago. The researchers realize there is much yet to learn about FIP, but the progress is encouraging.

“Antiviral drugs are not the end of FIP, and the disease will be with cat owners and veterinarians for a very long time,” Dr. Pedersen says. “The ultimate goal, of course, is to find ways to prevent the disease and not just treat it.

“We now know that FIP is a much more chronic disease than we originally assumed. In reality, FIP resembles chronic human infections such as tuberculosis or leprosy, with the infection staying localized and at a low level for weeks or even years. With time, the infection can weaken specific immune responses, causing clinical signs with severe immune reactions as the disease progresses.”

At Kansas State University, Dr. Kim plans to continue studying the progression of wet and dry FIP and the mechanisms that enable feline enteric coronavirus to mutate into FIP virus. Her objective is to discover more broad-spectrum antiviral compounds to fight multiple companion animal and human infections.

Dr. Pedersen aims to continue studying nucleoside analogs, hoping to find more effective treatments that can be given orally and are cheaper to produce. He also wants to better understand how FIP interacts with the immune system.

“We need to learn more about cats’ genetic susceptibility to the FIP virus,” he says. “Hopefully, we will discover effective ways to minimize feline enteric coronavirus infection and FIP in high-risk multicat environments, such as catteries, shelters and rescues. We do not know for certain that the FIP virus can ever be cleared from the body, but we suspect that cats that are still healthy after three months from ending treatment will stay healthy for the rest of their lives.”

The new antiviral drugs are not likely to be available for veterinarians CAT OWNERS CAN CONTRIBUTE TO BRIA FUND TO SUPPORT FIP RESEARCH
The Bria Fund was established by Susan Gingrich and her husband, Jim Shurskis, to support research of feline infectious peritonitis after their Birman kitten, Brieanna Jamie, died at 9 months of age from the disease. The couple, of Loudon, Tennessee, was devastated to lose the blue lynx-point kitten they had waited a year to get from a reputable Birman breeder.

In 2005, the Winn Feline Foundation began supporting FIP research through the Bria Fund. Since then, more than $569,000 has been raised to support 24 FIP studies. As a result of this research, significant advances have been made in understanding, diagnosing and treating FIP. The antiviral drug clinical trials of GS-441524 and GC376 covered in this issue of the Cat Update were funded in part by grants made possible from the Bria Fund.

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to use in their clinics for a few years, pending approval by the Food and Drug Administration. In the meantime, cat owners such as Roberts who were able to participate in the GS-441524 and GC376 clinical trials and whose cats achieved remission are grateful.

“We are blessed that Luna has done so well,” Roberts says. “She has been so active and social that we have started taking her on camping and hiking trips with us. We are thankful for the opportunity to have been part of the GS-441524 clinical trial and hope that others will benefit from this therapy. It has been a miracle for us and Luna.”

Purina appreciates the support of the Winn Feline Foundation, and particularly Vicki L. Thayer, DVM, DABVP (feline), former executive director, in helping to identify this topic for the Cat Update.
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