FIP treatment –
challenges and opportunities

Katrin Hartmann
Prof. Dr. med. vet., Dr. habil., Dipl. ECVIM-CA
FIP Treatment

Antiviral treatment
- ribavirin
- mefloquin
- itraconazol
- GC376
- remdesivir
- GS-441524

Outlook
FIP Treatment

antiviral treatment
- ribavirin
- mefloquin
- itraconazol
- GC376
- remdesivir
- GS-441524

outlook
Prognosis

so far deadly disease
→ median survival time 8 days
FIP Treatment

antiviral treatment
- ribavirin
- mefloquin
- itraconazol
- GC376
- remdesivir
- GS-441524

outlook
Ribavirin

experimental study

→ all cats died, treated cats had
  • more severe clinical signs
  • shorter mean survival time

many adverse effects

• hemolysis (drug sequestration in red blood cells)
• bone marrow toxicity
• liver toxicity

attempt to reduce toxicity (lecithin-containing liposomes)
→ also not effective

Weiss et al., 1993
FIP Treatment

antiviral treatment
- ribavirin
- mefloquin
- itraconazol
- GC376
- remdesivir
- GS-441524

outlook
Mefloquin

- used for prophylaxis and treatment of malaria in humans
- *in vitro* efficacy against FCoV without cytotoxic effects

- 2 studies on pharmacokinetics in clinically healthy cats
- adverse effects: vomiting after administration without food, increase in SDMA concentration (not creatinine)

McDonagh et al., 2011

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Animals

*Article*

**Pharmacokinetic Profile of Oral Administration of Mefloquine to Clinically Normal Cats: A Preliminary In-Vivo Study of a Potential Treatment for Feline Infectious Peritonitis (FIP)**

Jane Yu *, Benjamin Kimble, Jacqueline M. Norris* and Merran Govendir

**RESEARCH ARTICLE**

Assay validation and determination of *in vitro* binding of mefloquine to plasma proteins from clinically normal and FIP-affected cats

Aaron M. Izes*, Benjamin Kimble*, Jacqueline M. Norris*, Merran Govendir*
FIP Treatment

- antiviral treatment
  - ribavirin
  - mefloquin
  - itraconazol
  - GC376
  - remdesivir
  - GS-441524

outlook
Itraconazol

- antifungal drug and inhibitor of the cholesterol synthesis and transport
  - inhibits FCoV replication

- combination of GS-441524 with itraconazole in cell culture
  - synergistic antiviral effects
  - enhancement of antiviral effects of GS-441524 and inhibition of FCoV replication

Takano et al. 2017
Takano et al. 2019
Takano et al. 2019
FIP Treatment

**antiviral treatment**
- ribavirin
- mefloquin
- itraconazol
- GC376
- remdesivir
- GS-441524

**outlook**
Protease inhibitor GC376

protease inhibitor
→ developed by Gilead Sciences, USA
→ very effective *in vitro*, low cytotoxicity

experimental study
8 cats
- experimentally induced FIP
- all cats developed clinical signs
- 4 cats treated early, 4 cats treated late
- 6 cats in remission (2 euthanized)
  - 6 cats completely healthy (no signs or laboratory changes for 8 months)
  - drop in viral load (in the 2 euthanized cats)
Efficacy of a 3C-like protease inhibitor in treating various forms of acquired feline infectious peritonitis

Niels C Pedersen¹, Yunjeong Kim², Hongwei Liu¹, Anushka C Galasiti Kankanamalage³, Chrissy Eckstrand⁴, William C Groutas³, Michael Bannasch¹, Juliana M Meadows⁵ and Kyeong-Ok Chang²

- field study with protease inhibitor GC376
- 19/20 cats clinical remission within 2 weeks
- but relapses in 13/19 cats
- severe neurological signs in 8/13 cats
- 6 cats in remission at time of publication
- adverse effects:
  - pain at injection site
  - subcutaneous fibrosis and alopecia
  - abnormal eruption of teeth in cats aged < 16 – 18 weeks
Efficacy of a 3C-like protease inhibitor in treating various forms of acquired feline infectious peritonitis

Pedersen et al., 2018

6/20 cats in remission (1 year after therapy)
Resistance against GC376

• *in vitro* passage of wildtype FCoV (mutated strain) in presence of GC376
  → up to 3-fold resistance against multiple protease inhibitors
• GC376 not effective against these resistant mutants
FIP Treatment

antiviral treatment

- ribavirin
- mefloquin
- itraconazol
- GC376
- remdesivir
- GS-441524

outlook
Remdesivir versus GS-441524

remdesivir (GS-5734)
- monophosphoramide prodrug
- in the body metabolized to the active form GS-441524
- better intracellular transport through phosphorylation

triophosphate metabolite of both compounds
Remdesivir in cats

- broad-spectrum virostatic agent (originally for Ebola)
- developed by Gilead Sciences, USA
- marketed under the name Veklury® since mid-2020

- used in cats in Australia and UK
Remdesivir in cats

- homepage of the animal hospital Walkervillevet in Australia
- already approx. 30 cats suffering from FIP (diagnosis unknown) "successfully" treated with Remdesivir for 84 days
- relatively good tolerated
- adverse effects
  - temporary local irritation
  - pain during injection
  - development/exacerbation of pleural effusion within the first 48 hours
  - lethargy and nausea for several hours after IV administration

Successful treatment of a South African cat with effusive feline infectious peritonitis with remdesivir

- **case report** from South Africa
- treatment of a cat with effusion (FIP diagnosis by IHC from effusion cell pellet)
- 4.9-5.6 mg/kg q24h IV and SC for 30 days: 3 days IV, then SC
- after 1 week marked improvement of clinical signs, after 80 days cat in complete remission
- 7 months after end of treatment (at time of publication) still clinically unremarkable
Remdesivir in cats

- broad-spectrum virostatic agent (originally for Ebola)
- developed by Gilead Sciences, USA
- marketed under the name Veklury® since mid-2020
- used in cats in Australia and UK
- remdesivir injections:
  10 – 20 mg/kg IV q24h (dosage depending on clinical signs)
- costs: 390 US$ per vial with 100 mg remdesivir
- not stable after vial opened
- large fluid volume
FIP Treatment

- **antiviral treatment**
  - ribavirin
  - mefloquin
  - itraconazol
  - GC376
  - remdesivir
  - GS-441524

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

- nucleoside analogue GS-441524
- highly effective in vitro

- 12 cats with experimental FIP
- GS-441524 2 mg/kg q 24 h or 5 mg/kg SC q 24 h for 2 weeks

- all cats in remission (8 month after end of treatment)
- adverse effects: local irritation to SC injection
Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats with naturally occurring feline infectious peritonitis

Niels C Pedersen¹, Michel Perron², Michael Bannasch¹, Elizabeth Montgomery¹, Eisuke Murakami², Molly Liepnieks³ and Hongwei Liu³

- 31 field cats with FIP with and without effusion
- cats with neurological signs and/or uveitis excluded
- GS-441524 2 mg/kg SC q 24 h for at least 12 weeks (increased to 4 mg/kg in some cases)
- 26/31 cats GS for at least 12 weeks
- 8/26 with relapse
- adverse effects: painful injection site; 1 cat ↑BUN and SDMA

19/26 cats in remission
Antiviral treatment using the adenosine nucleoside analogue GS-441524 in cats with clinically diagnosed neurological feline infectious peritonitis

Peter J. Dickinson¹ | Michael Bannasch² | Sara M. Thomasy¹,³ |
Vishal D. Murthy² | Karen M. Vemau¹ | Molly Liepnieks⁴ |
Elizabeth Montgomery² | Kelly E. Knickelbein² | Brian Murphy⁴ | Niels C. Pedersen⁵

- 4 privately owned cats with FIP with neurological signs
- GS-441524 5 mg/kg SC q 24 h for at least 12 weeks (gradually increased to 10 mg/kg in one case)
- 3/4 cats alive 528, 516, and 354 days after initiation of treatment
- 1 cat euthanized on day 216 → relapse after 2 courses of treatment
online survey (393 participants) among cat owners

→ cats with suspected FIP

→ treatment with GS-441524 (via black market)

• 380 cats (88.2%) alive at time of publication
retrospective study: 141 cats with FIP (with effusion)
treated with Mutian® Xraphconn
116 cats (group 1) alive, 25 cats (group 2) died
comparison of the laboratory parameters
   → bilirubin as prognostic parameter
   (> 4.0 mg/dL → survival less likely)
Curing Cats with Feline Infectious Peritonitis with an Oral Multi-Component Drug Containing GS-441524

Daniela Krentz 1,*, Katharina Zenger 1, Martin Alberer 2, Sandra Felten 1, Michèle Bergmann 1, Roswitha Dorsch 1, Kaspar Matiasek 3, Laura Kolberg 4, Regina Hofmann-Lehmann 4, Marina L. Meli 4, Andrea M. Spiri 5, Jeannie Horak 5, Saskia Weber 6, Cora M. Holicki 6, Martin H. Groschup 6,7, Yury Zablotski 1, Eveline Lescrinier 4, Berthold Koletzko 5, Ulrich von Both 2,6,7, and Katrin Hartmann 1,6

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7 German Center for Infection Research (DZIF), Partner Site Hamburg-Lübeck-Borstel-Riems, Greifswald-Insel Riems, 17493 Greifswald, Germany
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11 These authors contributed equally to this work.


Academic Editors: Séverine Tasker and Julia A. Beatty

* Correspondence: d.krentz@medizinische-kleintierklinik.de
Aims of the study

1.) evaluation of the efficacy of Xraphconn® in FIP after oral administration
   - *in vitro* and *in vivo*

2.) analysis of the active ingredient in Xraphconn®

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Curing Cats with Feline Infectious Peritonitis with an Oral Multi-Component Drug Containing GS-441524

Daniela Krentz 1,4, Katharina Zenger 1, Martin Alberer 2, Sandra Felten 1, Michèle Bergmann 1, Roswitha Dorsch 1, Kaspar Matiasik 1, Laura Kolberg 1, Regina Hofmann-Lehmann 1, Marina L. Meli 4, Andra M. Spiri 4, Jeannie Horak 5, Saskia Weber 6, Cora M. Holicki 8, Martin H. Gruschup 5,7, Yury Zablotski 3, Eveline Lecharnier 8, Berthold Koletzko 5, Ulrich von Both 2,9,10, and Katrin Hartmann 1,4
What is Xraphconn®?

Figure 8. 13C spectrum of the analyzed sample. Labels refer to the assignment of carbons in the active component of Xraphconn® depicted above. All signals above 100 ppm belong to the cyano-group and nucleobase in the identified compound. Some additional signals of uncharacterized impurities were observed below 80 ppm (indicated with *). Ppm, parts per million.
oral treatment with Xraphconn® q24h for 84 days

all 18 cats completely cured
Clinical parameters
Laboratory parameters (1)
Laboratory parameters (2)
Viral load in blood

FCoV RNA loads (RT-qPCR):
- negative
- 1-1000 copies
- 1001-10,000 copies
- 10,001-10,000 copies
- 100,001-1 Mio copies
- >1 Mio-100 Mio copies
- >100 Mio copies
- Sample missing

Viral load in blood copy number/ml

Days after start of treatment:
- 0
- 2
- 4
- 7
- 14
- 28
- 56
- 83

Viral load in blood copy number/ml:
- 0
- 1x10^4
- 2x10^4
- 3x10^4
- 4x10^4

Days after start of treatment:
- 0
- 2
- 4
- 7
- 14
- 28
- 56
- 83
### Viral load in effusion

<table>
<thead>
<tr>
<th>Days after start of treatment</th>
<th>FCoV in effusion</th>
</tr>
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<tr>
<td>0</td>
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<td>NT</td>
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<td>28</td>
<td>NT</td>
</tr>
<tr>
<td>56</td>
<td>NT</td>
</tr>
<tr>
<td>83</td>
<td>NT</td>
</tr>
</tbody>
</table>

#### FCoV load (RT-qPCR)

- **negative**
- 1-1000 copies
- 1001-10000 copies
- 10'001-100000 copies
- 100001-1 mio copies
- >1 mio-100 mio copies
- >100 mio copies

- ✗: Effusion present but not puncturable
- NT: No effusion present

#### Graph

- **Viral load in effusion (copies/ml)**
- **Days after start of treatment**

---

**Note:**

- **Erguss**
- **Tage nach Studienbeginn**
- **Viral load**
- **FCoV**
- **in effusion**
- **days after start of treatment**
<table>
<thead>
<tr>
<th>adverse effects</th>
<th>number of cats</th>
<th>grade</th>
<th>median day of first appearance (range)</th>
<th>symptomatic treatment</th>
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<tbody>
<tr>
<td>Heinz body formation</td>
<td>1/18</td>
<td>moderate</td>
<td>83</td>
<td>S-adenosyl-methionine</td>
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<td>lymphocytosis</td>
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<td>mild</td>
<td>4.5 (2-83)</td>
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<td>6/14</td>
<td>moderate</td>
<td>1 (0-28)</td>
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<td></td>
<td>4/14</td>
<td>severe</td>
<td>1 (0-2)</td>
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<td>1/11</td>
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<td>4</td>
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<tr>
<td></td>
<td>2/11</td>
<td>severe</td>
<td>4</td>
<td>silymarin</td>
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</tbody>
</table>
Article

Fecal Feline Coronavirus RNA Shedding and Spike Gene Mutations in Cats with Feline Infectious Peritonitis Treated with GS-441524

Marina L. Meli 1,*©, Andrea M. Spiri 1©, Katharina Zwicklbauer 2, Daniela Krentz 2©, Sandra Felten 2, Michele Bergmann 2, Roswitha Dorsch 2©, Kaspar Matiasek 3, Martin Alberer 4, Laura Kolberg 4©, Ulrich von Both 4,5©, Katrin Hartmann 2,†© and Regina Hofmann-Lehmann 1,†©

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4 Division of Paediatric Infectious Diseases, Dr. von Hauner Children’s Hospital, University Hospital, LMU-Munich, D-80337 Munich, Germany; martin.alberer@lrz.uni-muenchen.de (M.A.); laura.kolberg@med.uni-muenchen.de (L.K.); ulrich.von.both@med.lmu.de (U.v.B.)
5 German Center for Infection Research (DZIF), Partner Site Munich, D-80337 Munich, Germany
* Correspondence: mmeli@vetclinics.uzh.ch
† These authors contributed equally to this work.
FCoV load in feces

- 61% (11/18 cats) shedding FCoV within the first 3 days
- significant decrease in frequency of cats shedding FCoV by day 4 ($p = 0.040$)
- stop of shedding by day 6 but re-shedding in one cat

Adapted from Meli et al., 2022

T8, T10, T12, T17, T18 no detection of fecal shedding

T4

T9

T11
## S-Gene Sequencing

<table>
<thead>
<tr>
<th>Effusion</th>
<th>Blood</th>
<th>Feces</th>
<th>Cat Nr</th>
<th>Diverse timepoints</th>
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<tr>
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<tr>
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<td></td>
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<tr>
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<td>LS</td>
<td>LS</td>
<td>LS</td>
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<tr>
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<td>T18</td>
<td>LS</td>
<td>LS</td>
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</tbody>
</table>

- **Cat Nr**: Different samples with varying cat numbers.
- **Diverse timepoints**: Events and results over different time points.
- **Effusion**: Sample types include **LS** (Leucin 1058/Serine 1060), **FS** (Phenylalanin 1058/Serine 1060), **MA** (Methionine 1058/Alanine 1060), and **MS** (Methionine 1058/Serine 1060).
- **Blood** and **Feces** columns indicate sample types for these categories.
- **No companion cat**: Indicates a lack of companion cat samples.
- **No sampling**: Absence of sampling events.
- **Negative, no material, no band or too low viral load**: Indicates negative results due to insufficient material or viral load.

### Genetic Variants
- **Leucin 1058/Serine 1060 (M1)**
- **Phenylalanin 1058/Serine 1060 (M2)**
- **Methionine 1058/Alanine 1060 (new mutation)**
- **Methionine 1058/Serine 1060 (wild type)**
Long-term follow-up of cats in complete remission after treatment of feline infectious peritonitis with oral GS-441524

Katharina Zwicklbaumer, Daniela Krentz, Michèle Bergmann, Sandra Felten, Roswitha Dorsch, Andrea Fischer, Regina Hofmann-Lehmann, Marina L Meli, Andrea M Spiriti, Martin Alberer, Laura Kolberg, Kaspar Matiasek, Yury Zablotski, Ulrich von Both and Katrin Hartmann
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<th>parameters</th>
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<th>follow-ups</th>
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<td>D1</td>
<td>D2</td>
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<td>2nd follow-up (9 months)</td>
<td>3rd follow-up (12 months)</td>
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<td>15/18</td>
<td>14/18</td>
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<td>2/18</td>
<td>3/18</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCoV in blood</td>
<td>1/18 (CT 38.0)</td>
<td>0/15</td>
<td>0/14</td>
<td></td>
</tr>
<tr>
<td>FCoV in effusion</td>
<td>0/18</td>
<td>0/15</td>
<td>0/14</td>
<td></td>
</tr>
<tr>
<td>FCoV in feces</td>
<td>2/18</td>
<td>2/15</td>
<td>5/14</td>
<td></td>
</tr>
<tr>
<td>FCoV antibodies in serum</td>
<td>18/18</td>
<td>14/15</td>
<td>13/14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; follow-up (6 months)</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; follow-up (9 months)</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; follow-up (12 months)</td>
<td></td>
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<tr>
<td>--------------------------</td>
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<td>--------------------------------------</td>
<td>--------------------------------------</td>
<td></td>
</tr>
<tr>
<td>participating cats</td>
<td>18/18</td>
<td>15/18</td>
<td>14/18</td>
<td></td>
</tr>
<tr>
<td>missing owner compliance</td>
<td>0/18</td>
<td>2/18</td>
<td>3/18</td>
<td></td>
</tr>
<tr>
<td>death</td>
<td>0/18</td>
<td>1/18 (road traffic accident)</td>
<td>1/18</td>
<td></td>
</tr>
<tr>
<td>cats in complete remission</td>
<td>18/18</td>
<td>18/18</td>
<td>18/18</td>
<td></td>
</tr>
<tr>
<td>lymphadenomegaly</td>
<td>9/18</td>
<td>5/15</td>
<td>6/14</td>
<td></td>
</tr>
<tr>
<td>neurological signs (FHS)</td>
<td>0/18</td>
<td>1/15</td>
<td>2/14</td>
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</tbody>
</table>
Feline hyperesthesia syndrome (FHS)

in 2 cats new onset of neurological signs resembling feline hyperesthesia syndrome (FHS)

Diego, 2 years, Maine-Coon, male, neutered

Tina, 4.5 years, DSH, female, neutered
„Gusti“

DSH, 6 months, male, neutered
- recurrent fever
- lethargy, inappetence
- uveitis left

enucleation of the left eye

immunohistochemistry → FCoV-antigen positive

Case Report
Clinical Follow-Up and Postmortem Findings in a Cat That Was Cured of Feline Infectious Peritonitis with an Oral Antiviral Drug Containing GS-441524

Daniela Krentz 1,*,†, Katharina Zwicklbauer 1,*, Sandra Felten 1, Michèle Bergmann 1, Roswitha Dorsch 1, Regina Hofmann-Lehmann 2,†, Marina L. Meli 2, Andrea M. Spiri 2, Ulrich von Both 3, Martin Alberer 3, Anne Hönl 1,4, Kaspar Matiasek 4,† and Katrin Hartmann 1,†
course: fatal car accident 164 days after end of treatment
## IHC and RT-PCR

### in different tissues

<table>
<thead>
<tr>
<th>tissue</th>
<th>IHC for FCoV antigen</th>
<th>FCoV RT-qPCR (viral load)</th>
<th>18S rRNA RT-qPCR (control) CT-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inn. mand.</td>
<td>negative</td>
<td>negative</td>
<td>34.27</td>
</tr>
<tr>
<td>jejunum</td>
<td>negative</td>
<td>negative</td>
<td>35.90</td>
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<tr>
<td>duodenum</td>
<td>negative</td>
<td>negative</td>
<td>16.81</td>
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<tr>
<td>spleen</td>
<td>negative</td>
<td>negative</td>
<td>24.21</td>
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<tr>
<td>colon</td>
<td>negative</td>
<td>negative</td>
<td>34.49</td>
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<tr>
<td>Inn. mesent.</td>
<td>negative</td>
<td>negative</td>
<td>21.66</td>
</tr>
<tr>
<td>kidney</td>
<td>negative</td>
<td>negative</td>
<td>23.87</td>
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<tr>
<td>caecum</td>
<td>negative</td>
<td>negative</td>
<td>13.81</td>
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<tr>
<td>rectum</td>
<td>negative</td>
<td>negative</td>
<td>13.98</td>
</tr>
<tr>
<td>liver</td>
<td>negative</td>
<td>negative</td>
<td>23.43</td>
</tr>
<tr>
<td>brain</td>
<td>negative</td>
<td>negative</td>
<td>19.91</td>
</tr>
</tbody>
</table>
FIP Treatment

- antiviral treatment
  - ribavirin
  - mefloquin
  - itraconazol
  - GC376
  - remdesivir
  - GS-441524

- outlook
SCIENCE
A Much-Hyped COVID-19 Drug Is Almost Identical to a Black-Market Cat Cure

Cat owners are resorting to China’s underground marketplace to buy antivirals for a feline coronavirus.

SARAH ZHANG  MAY 8, 2020

Gilead invented and patented GS-441524, too. Its scientists co-authored the UC Davis studies showing effectiveness against FIP. But the company has refused to license GS-441524 for animal use, out of fear that its similarity to remdesivir could interfere with the human drug’s FDA-approval process—originally for Ebola. When that failed, and a global pandemic of a novel coronavirus later arose, the company began testing it against COVID-19. Remdesivir has a small but clever modification that makes it better at entering cells, but it and GS-441524 work in exactly the same way to inhibit viruses.
Outlook

- new study on 770 cats with BOVA GS-441524
  - 400 in Munich and 370 in Zurich
  - aim: evaluation of prognostic parameter
  - study approved by animal use committee
  - study just started 😊
  - no limitations for inclusion of cats (besides FIP)
  - few rechecks at university institutions
  - reduced costs

- contact
  - Munich: fip@medizinische-kleintierklinik.de
  - Zurich: fiptx@vetlabor.ch
Thank you for your attention!

and to the …

most amazing FIP/coronavirus team