# SFTSに関する治療薬・ワクチン開発

国立感染症研究所ウイルス第一部
吉河智城

# 重症熱性血小板減少症候群

1. 特徴
2. 治療薬
3. ワクチン開発

# 1. 特徴

# 発見

N Engl J Med 2011;364:1523-32.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Fever with Thrombocytopenia Associated with a Novel Bunyavirus in China

Mysterious diseases in mountainous regions Hubei and Henan provinces in China since 2008 – 2009

# 日本でのSFTS患者の確認

MAJOR ARTICLE

J Infect Dis. 2014 Mar;209(6):816-27.

## The First Identification and Retrospective Study of Severe Fever With Thrombocytopenia Syndrome in Japan

Toru Takahashi,[1,a] Ken Maeda,[4,a] Tadaki Suzuki,[6,a] Aki Ishido,[1] Toru Shigeoka,[1] Takayuki Tominaga,[1] Toshiaki Kamei,[2] Masahiro Honda,[3] Daisuke Ninomiya,[12] Takenori Sakai,[12] Takanori Senba,[12] Shozo Kaneyuki,[14] Shota Sakaguchi,[15] Akira Satoh,[16] Takanori Hosokawa,[18] Yojiro Kawabe,[19] Shintaro Kurihara,[17] Koichi Izumikawa,[17] Shigeru Kohno,[17] Taichi Azuma,[13] Koichiro Suemori,[13] Masaki Yasukawa,[13] Tetsuya Mizutani,[10] Tsutomu Omatsu,[10] Yukie Katayama,[10] Masaharu Miyahara,[20] Masahito Ijuin,[22] Kazuko Doi,[21] Masaru Okuda,[5] Kazunori Umeki,[11] Tomoya Saito,[11] Kazuko Fukushima,[11] Kensuke Nakajima,[11] Tomoki Yoshikawa,[7] Hideki Tani,[7] Shuetsu Fukushi,[7] Aiko Fukuma,[7] Momoko Ogata,[7] Masayuki Shimojima,[7] Noriko Nakajima,[6] Noriyo Nagata,[6] Harutaka Katano,[6] Hitomi Fukumoto,[6] Yuko Sato,[6] Hideki Hasegawa,[6] Takuya Yamagishi,[8] Kazunori Oishi,[8] Ichiro Kurane,[7] Shigeru Morikawa,[9] and Masayuki Saijo[7]

患者は2005年まで遡って確認されている

# 臨床症状


病態はクリミアコンゴ出血熱に類似

# 致命率

中国の論文
21/171 (12%)

日本での研究
approx. 400 cases (2014–2019)
CFR 27%

韓国では
33%

# 媒介動物

## マダニ

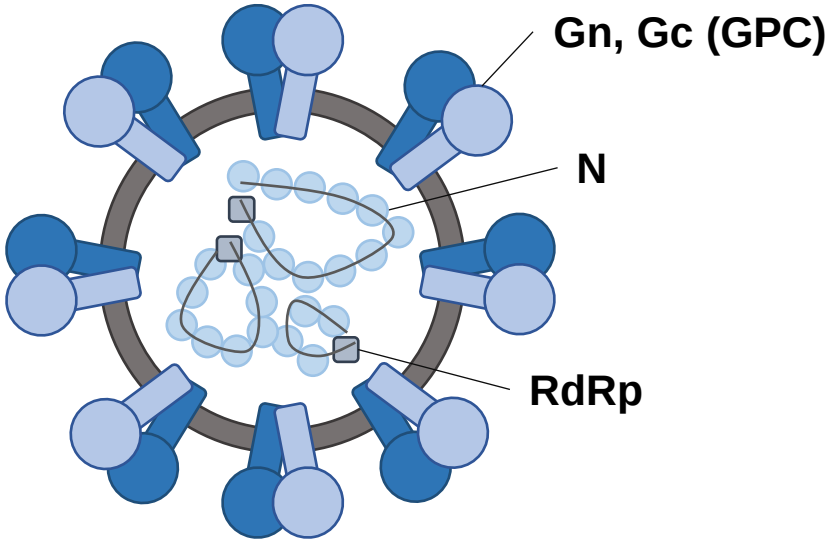
*Haemaphysalis longicornis*

但し、ダニ刺咬痕は患者の半数程度にのみ存在

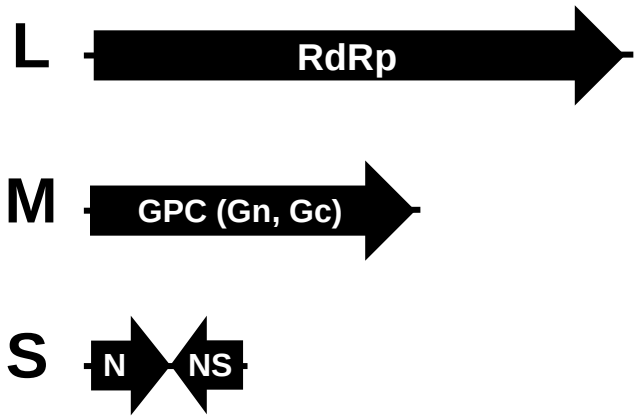
伴侶動物を介した感染も報告されている

# SFTSウイルス

## Virion




## Genome




## Characters

# SFTS患者が報告された国

# SFTS患者の年齢分布

表1. 基本情報（2020年12月30日現在）

| | | 生存例 | 死亡例 | 合計 |
|---|---|---|---|---|
| **報告数** | | 498 | 75 | 573 |
| **性別** | 男 | 244 | 42 | 286 |
| | 女 | 254 | 33 | 287 |
| **年齢** | 中央値 | 73 歳 | 81 歳 | 74 歳 |
| | ～20代 | 5 | 0 | 5 |
| | 30代 | 9 | 0 | 9 |
| | 40代 | 13 | 0 | 13 |
| | 50代 | 34 | 3 | 37 |
| | 60代 | 125 | 11 | 136 |
| | 70代 | 162 | 21 | 183 |
| | 80代 | 129 | 34 | 163 |
| | 90代～ | 21 | 6 | 27 |

注）死亡数は感染症発生動向調査の届出時点での情報であることから、正確な死亡数及び算出される致命率はより高い可能性がある．また自治体による公表情報とは異なる場合がある．

感染症発生動向調査（https://www.niid.go.jp/niid/ja/diseases/sa/sfts.html）より

# 2. 治療薬

# Efficacy of favipiravir (T-705) against severe fever with thrombocytopenia syndrome virus infection

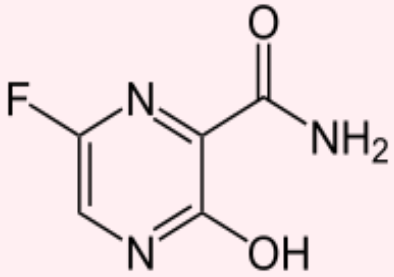
**Hideki Tani[1], Shuetsu Fukushi[1], Aiko Fukuma[1], Satoshi Taniguchi[1], Tomoki Yoshikawa[1], Naoko Iwata-Yoshikawa[2], Noriyo Nagata[2], Akihiko Uda[3], Shigeru Morikawa[3], Takashi Komeno[4], Yousuke Furuta[4], Masayuki Shimojima[1], Masayuki Saijo[1]**

***[1]Department of Virology I , [2]Department of Pathology, [3]Department of Veterinary Science, National Institute of Infectious Diseases, Tokyo***

***[4]Research Laboratories, Toyama Chemical Co., Ltd., Toyama, Japan***

# T-705
# (Favipiravir)

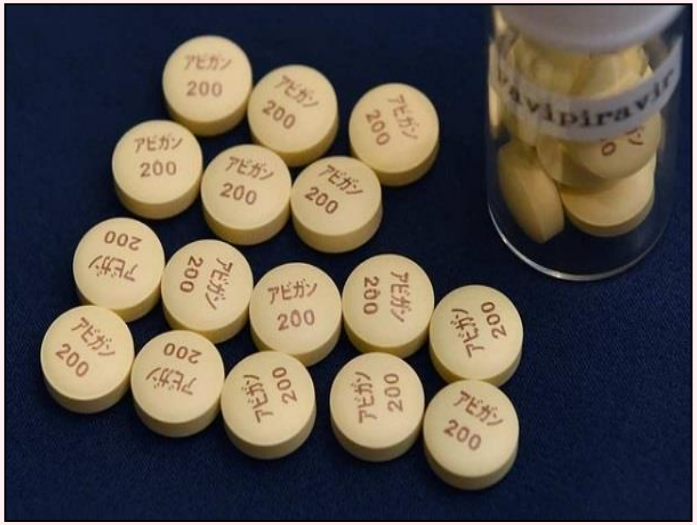
- **A novel antiviral drug (Avigan® ) for the treatment of influenza**




$C_5H_4FN_3O_2$

- **Developed in Japan by Toyama Chemical Co., Ltd.**

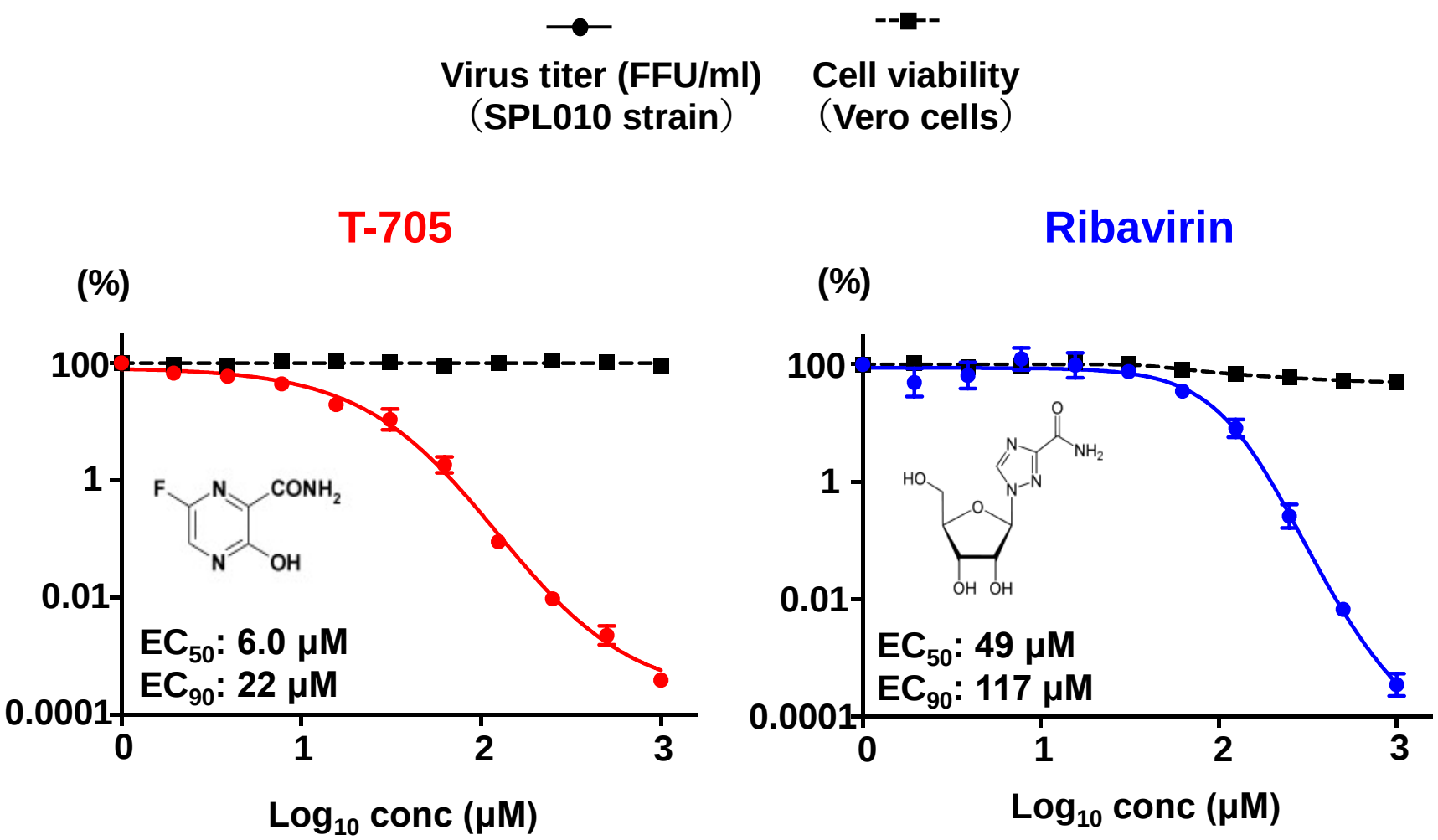
- **Inhibits the RNA polymerase of various RNA viruses (e.g. Ebola virus)**



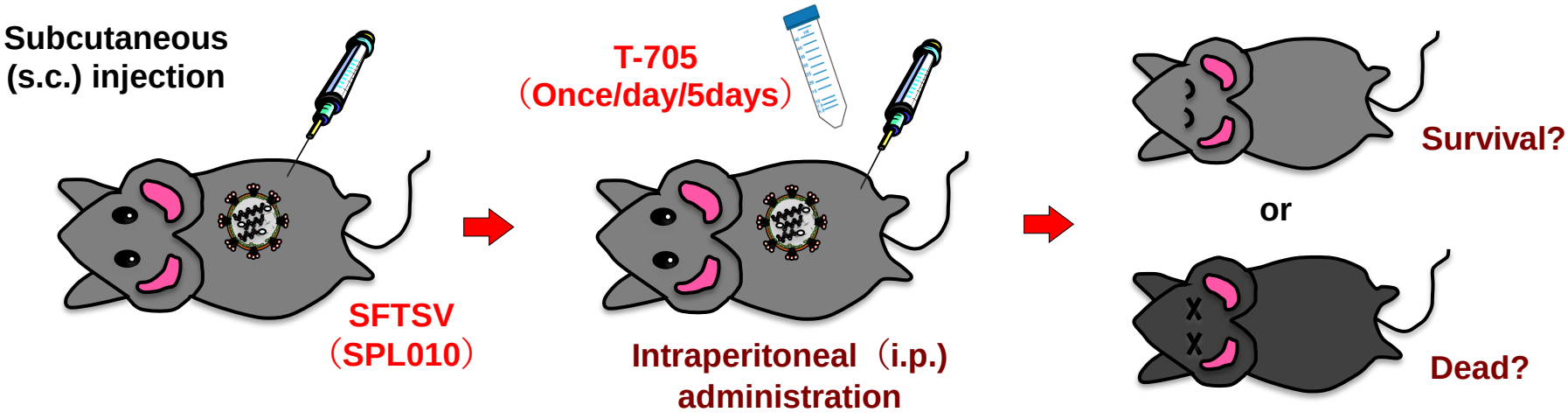
# Inhibitory effects of T-705 on RNA virus infections *in vitro*

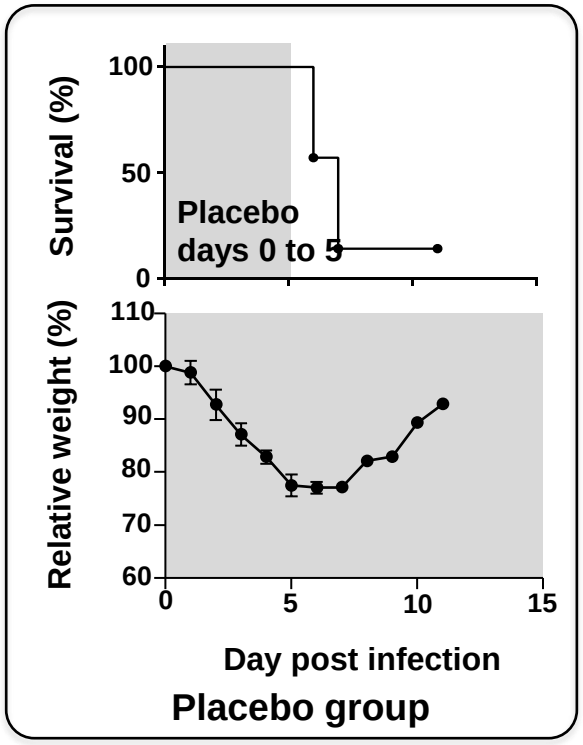
| Group | Family | Virus | EC50 (μg/mL) | Reference |
|---|---|---|---|---|
| (+) strand RNA virus | Flaviviridae | West Nile virus | 53 | Antiviral Res. 2008 |
| | | Yellow fever virus | 42 | Antimicrob Agents Chemother. 2009 |
| | Togaviridae | Western equine encephalitis virus | 49 ($EC_{90}$) | Antiviral Res. 2009 |
| | | Chikungunya virus | 0.3-9.4 | J Antimicrob Chemother. 2014 |
| | Picornaviridae | Poliovirus | 4.8 | Antimicrob Agents Chemother. 2002 |
| | | Rhinovirus | 23 | Antimicrob Agents Chemother. 2002 |
| | Caliciviridae | Norovirus | 13-25 | Biochem Biophys Res Commun. 2012 |
| (-) strand RNA virus | Orthomyxoviridae | Influenza A virus (seasonal) | 0.01-0.94 | Antimicrob Agents Chemother. 2002, 2010 |
| | | Influenza A virus (H5N1) | 0.2-1.9 | Antimicrob Agents Chemother. 2007, 2010 |
| | | Influenza A virus (H7N9) | 0.38-0.74 | Antivir Chem Chemother. 2014 |
| | | Influenza B virus | 0.04-0.8 | Antimicrob Agents Chemother. 2002, 2010 |
| | | Influenza C virus | 0.03-0.06 | Antimicrob Agents Chemother. 2002 |
| | Paramyxoviridae | Respiratory syncytial virus | 41 | Antimicrob Agents Chemother. 2002 |
| | Bunyaviridae | La Crosse virus | 5 | Antimicrob Agents Chemother. 2007 |
| | | Rift Valley fever virus | 4.2-5.0 | Antimicrob Agents Chemother. 2007, Antiviral Res. 2010 |
| | | Sandfly fever virus | 4.7-18 | Antimicrob Agents Chemother. 2007, Antiviral Res. 2010 |
| | | Andes virus | 2.5-5.0 ($EC_{90}$) | Antimicrob Agents Chemother. 2013 |
| | | Crimean-Congo hemorrhagic fever virus | 0.6-2.8 | PLoS Negl Trop Dis. 2014 |
| | Arenaviridae | Junin (Candid 1) | 0.8-1.4 | Antimicrob Agents Chemother. 2007, Antiviral Res. 2010 |
| | | Pichinde | 0.9-3.9 | Antimicrob Agents Chemother. 2007, Antiviral Res. 2010 |
| | | Guanarito | 2.6 | Antimicrob Agents Chemother. 2011 |
| | | Machupo | 2.2 | Antimicrob Agents Chemother. 2011 |
| | Filoviridae | Ebola | 10.5 | Antiviral Res. 2014 |

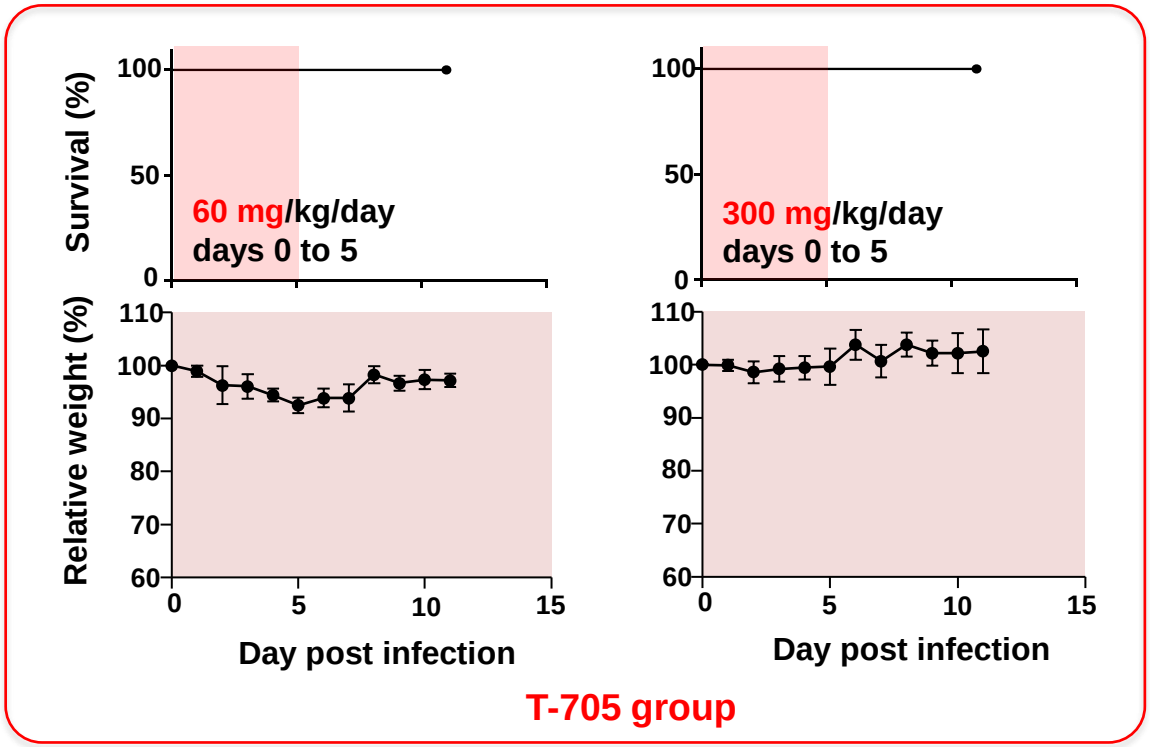
# Inhibitory effects of T-705 and ribavirin on SFTSV infection in Vero cells



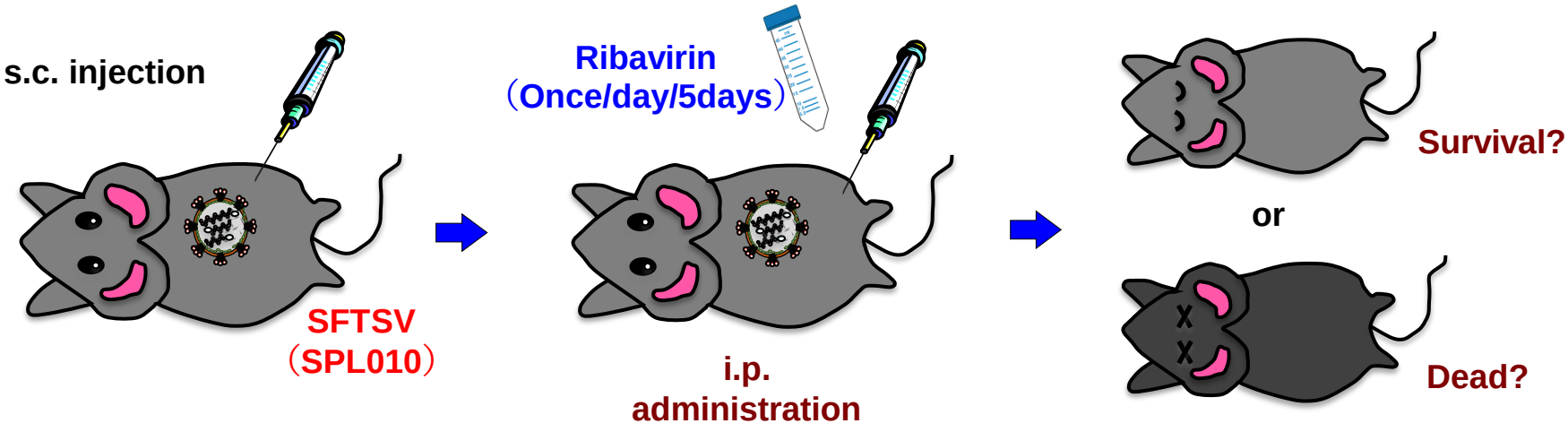
# Treatment of SFTSV-infected IFNAR$^{-/-}$ mice with T-705

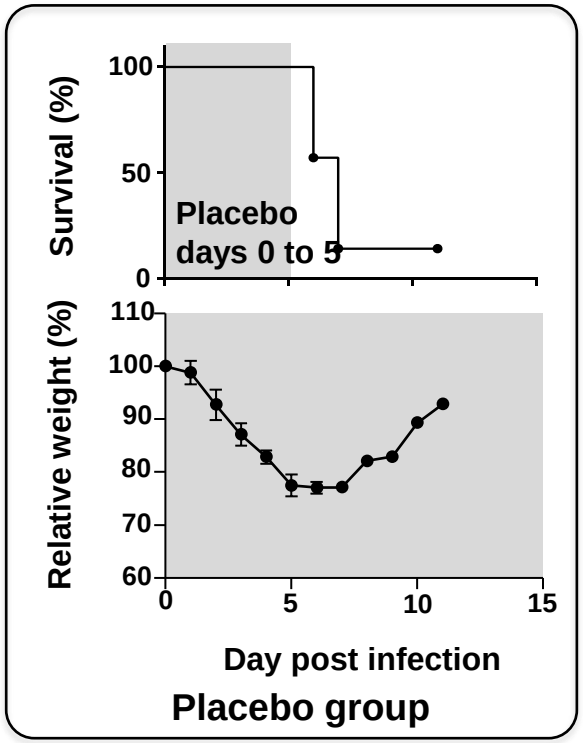


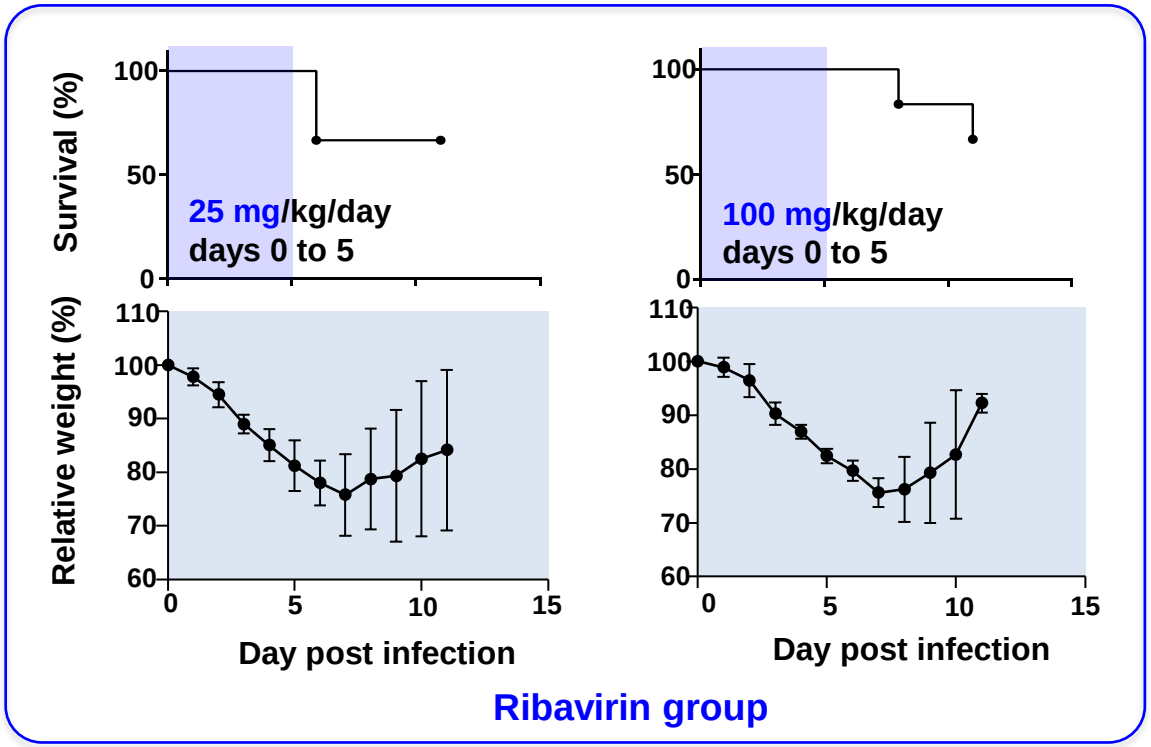



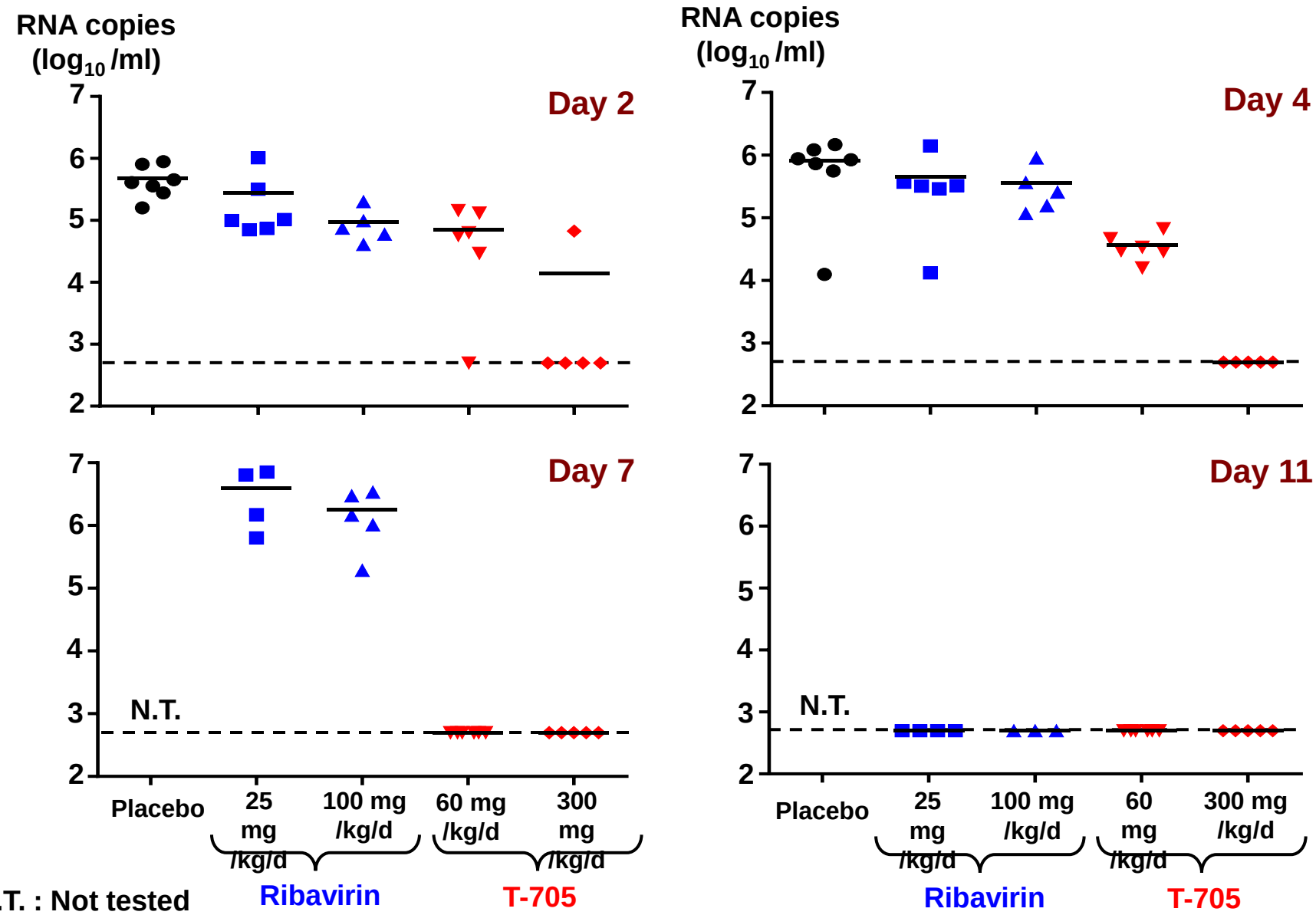
# Treatment of SFTSV-infected IFNAR$^{-/-}$ mice with ribavirin



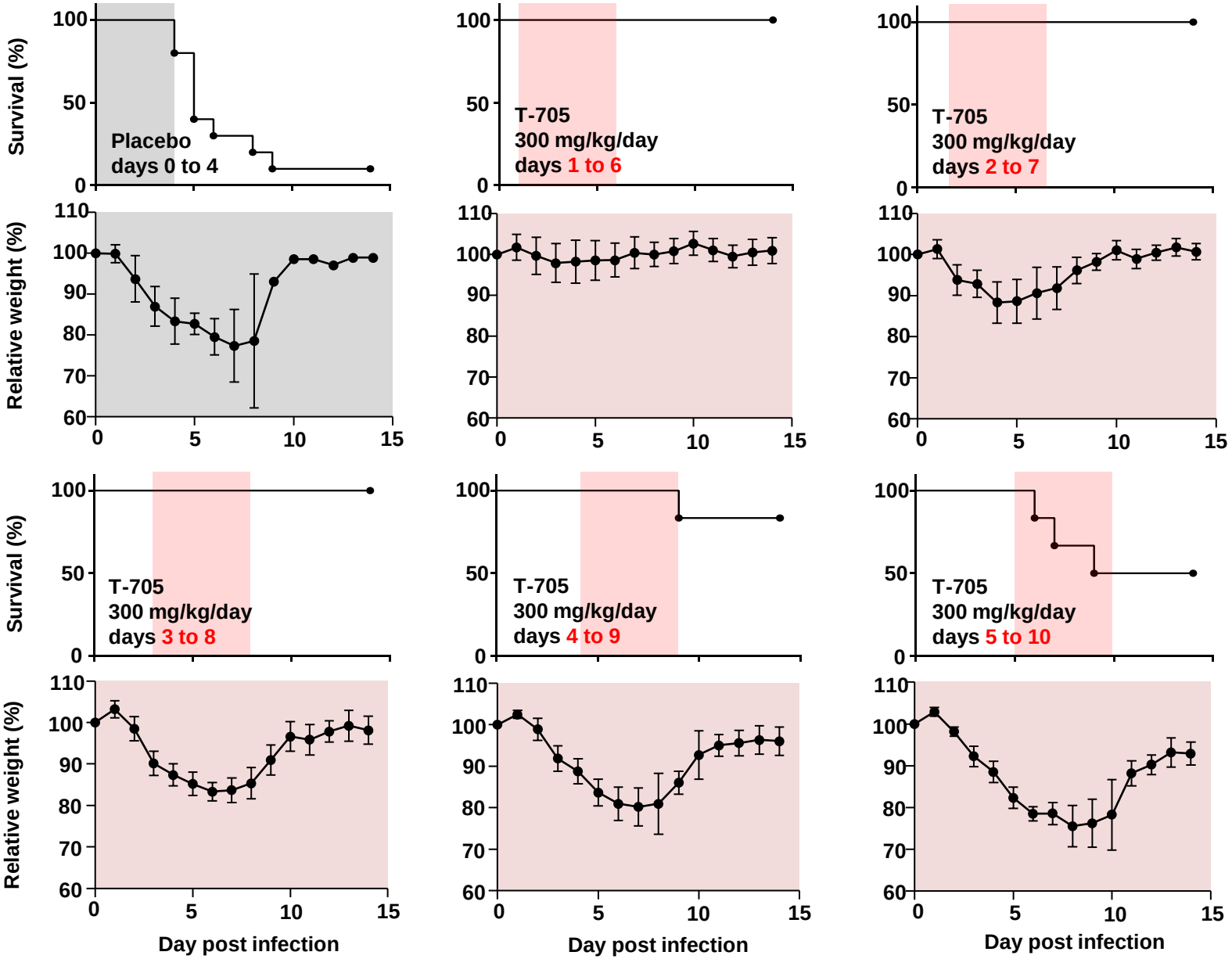



# SFTSV RNA levels in the blood samples of SFTSV-infected IFNAR$^{-/-}$ mice




N.T. : Not tested

# Therapeutic efficacy of T-705 in SFTSV-infected IFNAR$^{-/-}$ mice



# ヒトでの臨床研究結果が掲載されます

**A multicenter non-randomized, uncontrolled single arm trial for evaluation of the efficacy and the safety of the treatment with favipiravir for patients with severe fever with thrombocytopenia syndrome**

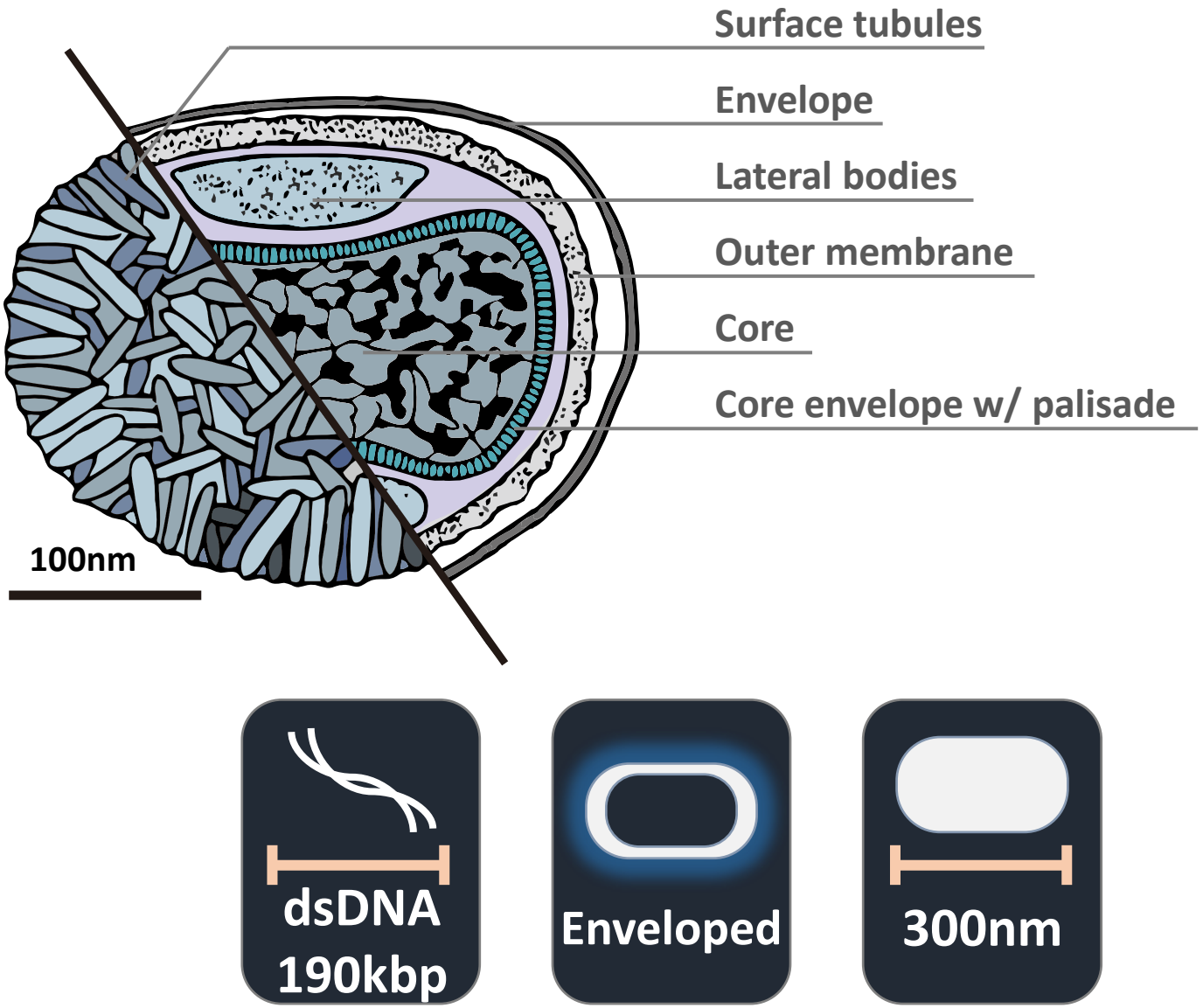
**PLOS Neglected Tropical Diseases**
**in press**

感染研ウイルス第一部を含む17のグループで行われた臨床研究

本臨床研究にてファビピラビルの経口投与を受けたSFTS患者の投与開始後28日間での致命率は17.3%となり、国内の致命率27%を下回った

# 3. ワクチン開発

# Vaccinia Virus: A Recombinant Vaccine Vector

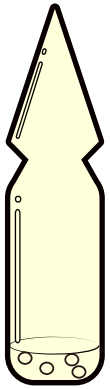



Modified form Dubochet, et al., J. Virol. 1994

# A Smallpox Vaccine Strain, LC16m8 (m8)

Effective

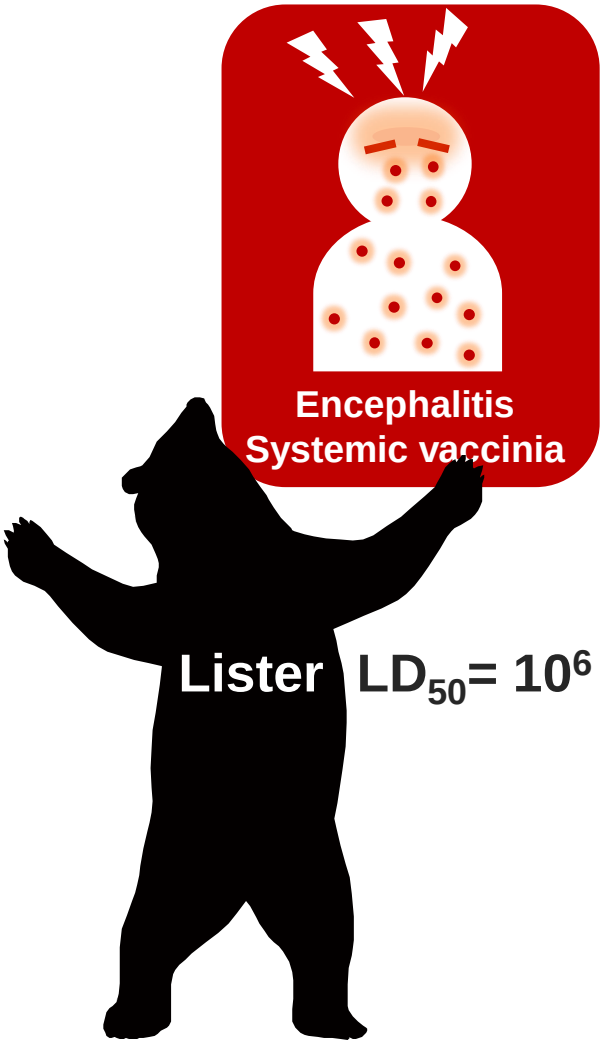

ation



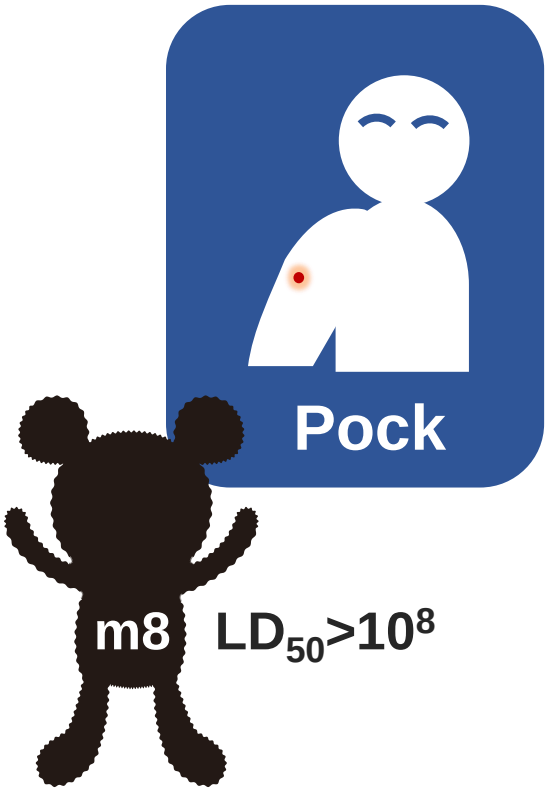
Can be lyophilized

# 3rd Generation is Highly Attenuated

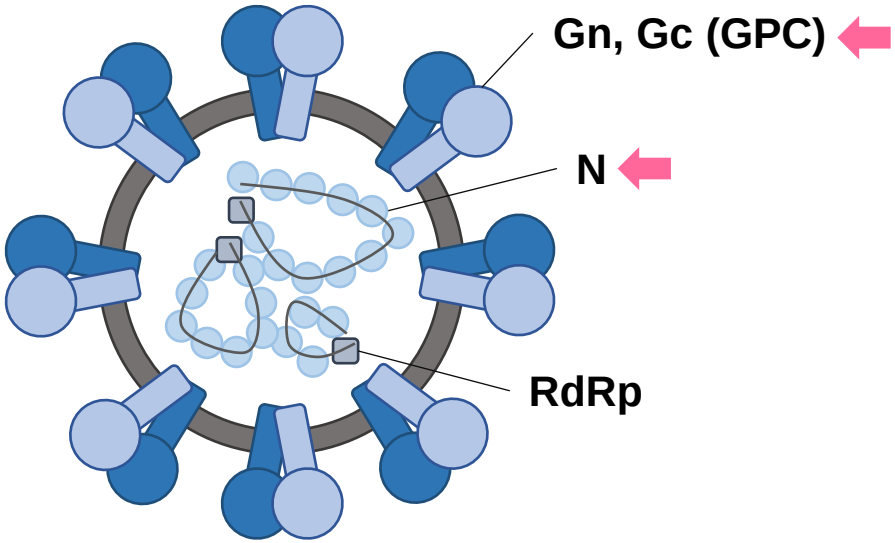
## 2nd generation



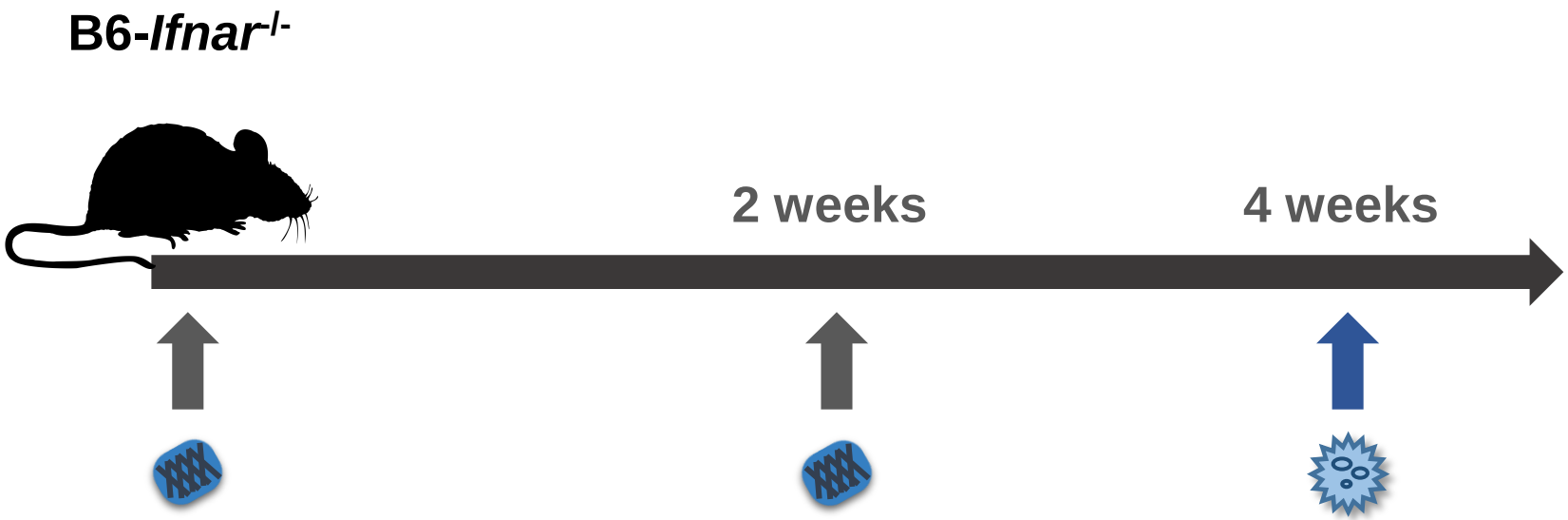

## 3rd generation



# Vaccine Target



# Vaccine Efficacy of Recombinant m8s

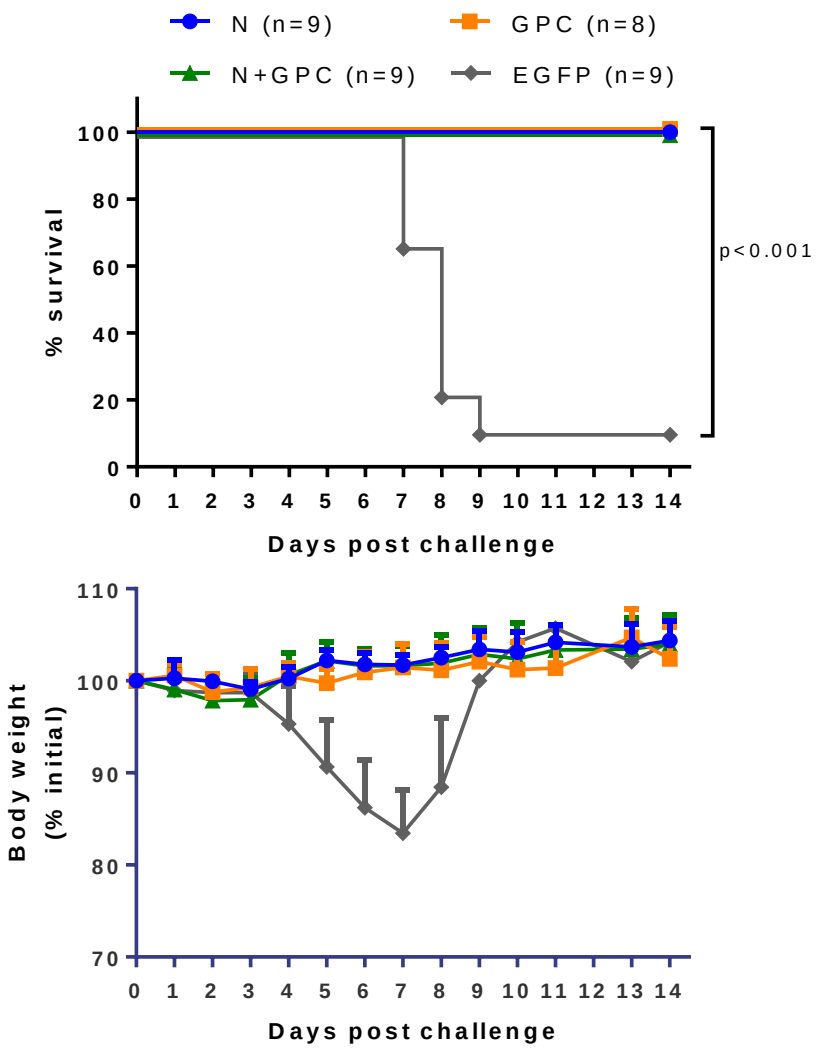



**m8-EGFP**
**m8-SFTSV-N**
**m8-SFTSV-GPC**
**m8-SFTSV–N+GPC**
**1x10$^{6}$ PFU/100ul/s.c.**

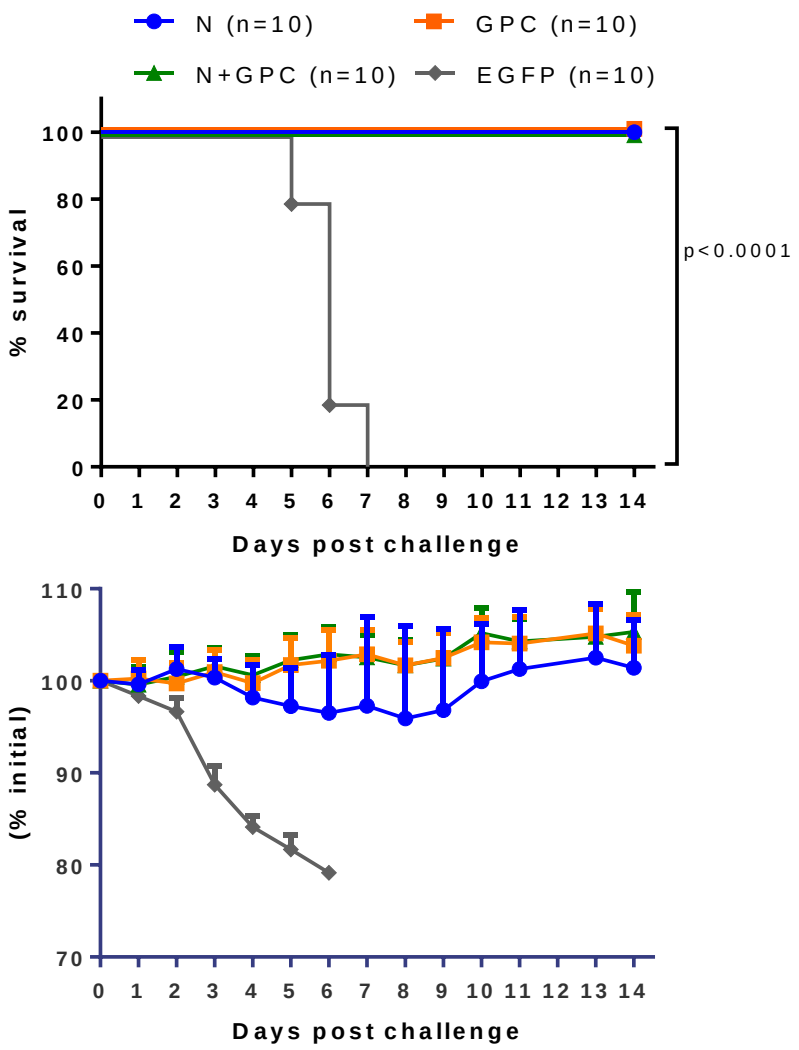
**SFTSV**
**YG-1**
**1x10$^{3}$ or 1x 10$^{5}$ $TCID_{50}$**
**/100ul s.c.**

# The Result

## SFTSV $10^3$ $TCID_{50}$ challenge




## SFTSV $10^5$ $TCID_{50}$ challenge



# マウスを用いた研究成果が掲載されました

**A highly attenuated vaccinia virus strain LC16m8-based vaccine for severe fever with thrombocytopenia syndrome**

**PLOS Pathogens**
**2021 Feb 3;17(2):e1008859.**
**PMID: 33534867**

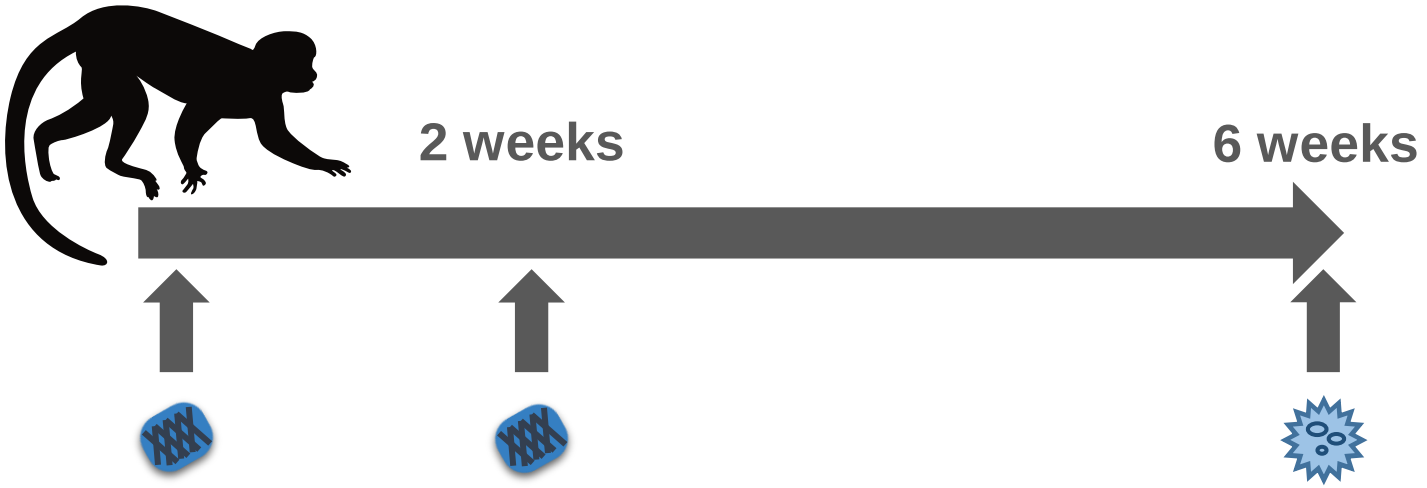
m8-SFTSワクチンはどのような性状なのか？

ワクシニア事前接種済みのマウスにm8-SFTSワクチンは有効か？

m8-SFTSワクチンにより誘導される有効な獲得免疫は何か？

# The Vaccine Efficacy in Monkeys

6 cynomolgus macaques
4 males, 2 females

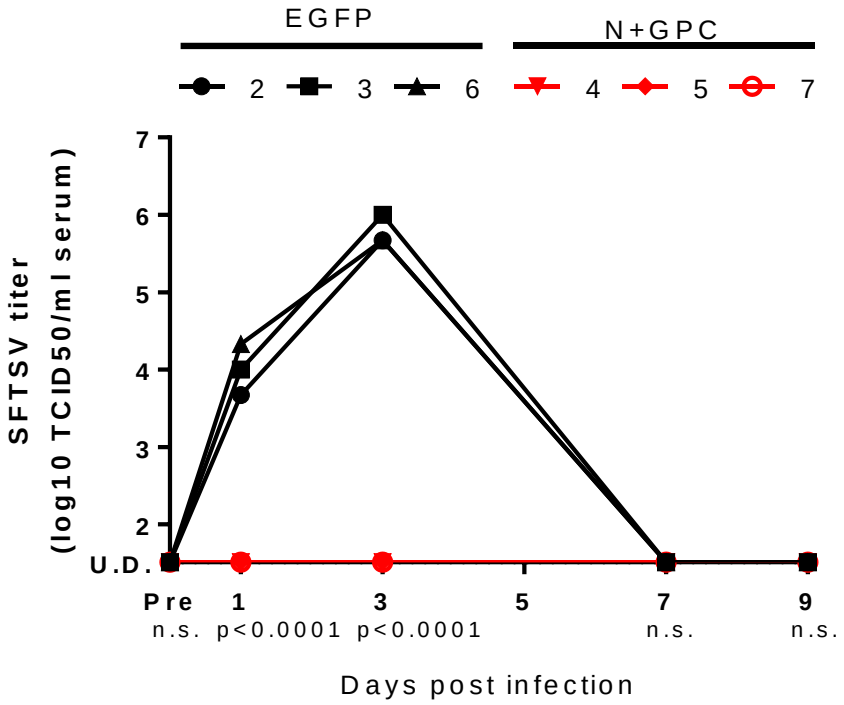



**m8-EGFP (n=3)**
**m8-N+GPC (n=3)**
**$1x10^7$ PFU/100μl, i.d.**

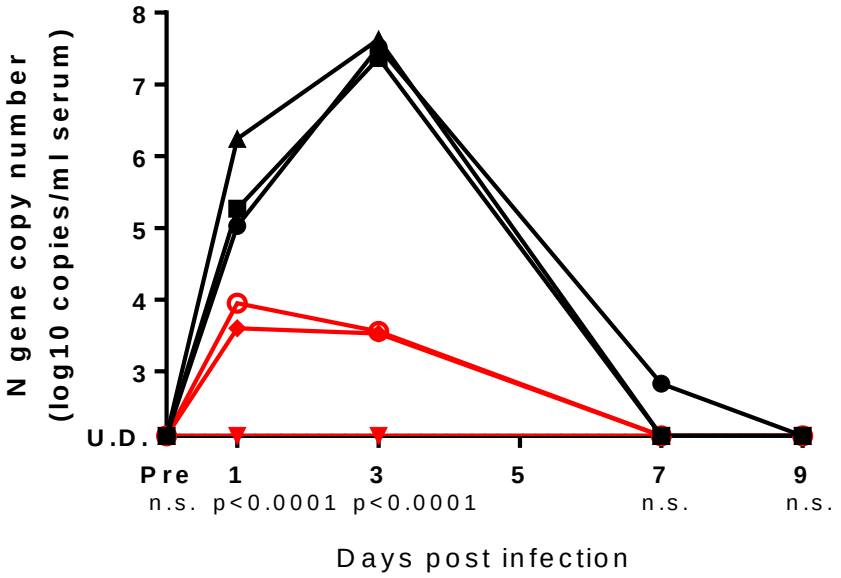
**SFTSV**
**SPL10**
**$1x10^9$ $TCID_{50}$/5ml, i.v.**

# SFTS Viral Load in Sera

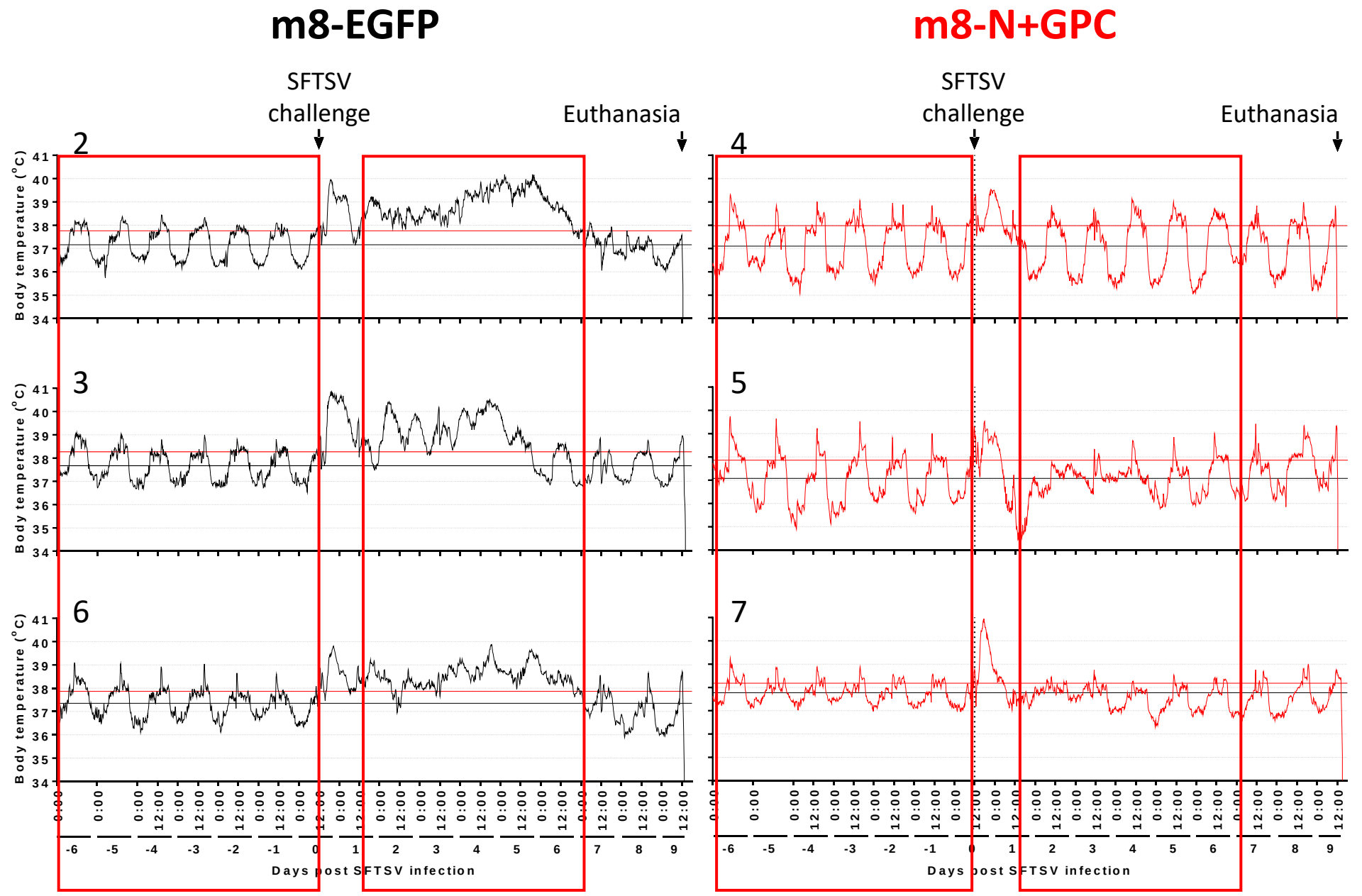
## SFTSV titer




## SFTSV gene copies



# Body Temperature



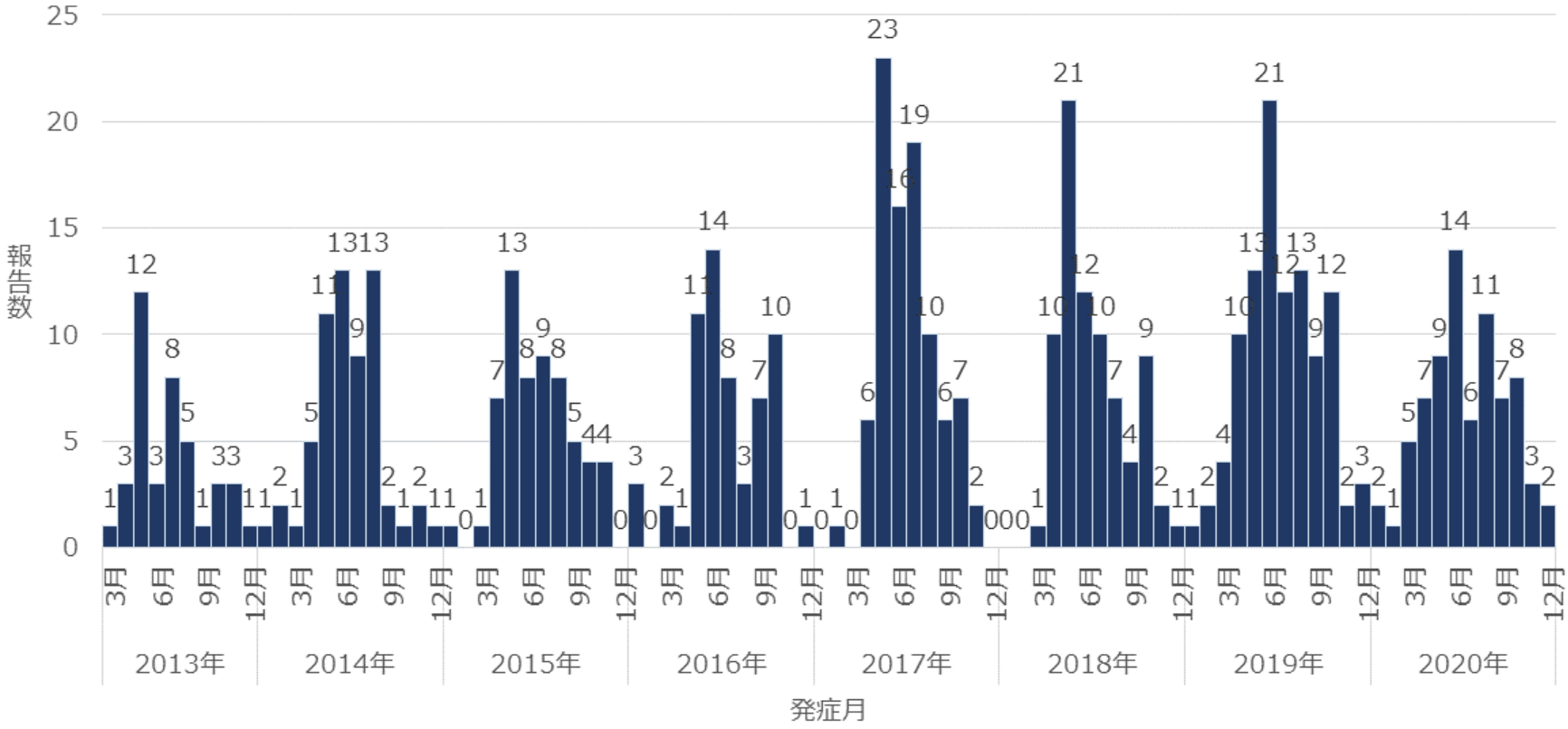
# 最後に

# SFTS症例の推移

図1．2013年3月4日以降に届出られたSFTS症例の発症時期（n=565, 2020年12月30日現在）

※届出対象となる日時以前の発症例8例を除く

（SFTSは2013年3月4日に感染症法で全数把握対象疾患である4類感染症に指定された）




感染症発生動向調査（https://www.niid.go.jp/niid/ja/diseases/sa/sfts.html）より