JRPI

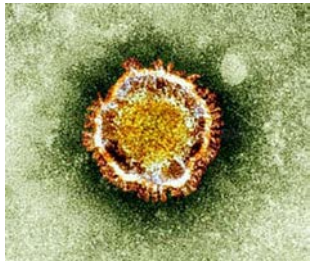
XX[e] Journée Régionale

de Pathologie Infectieuse

Session Coronavirus

Pistes thérapeutiques

B Guery



Therapeutic challenge for MERS-CoV

- ✓ Antiviral activity
  - Ribavirin
  - Lopinavir
  - Interferon
  - Cyclosporin A
  - Associations
  - Protease inhibition
  - Monoclonal antibodies
- ✓ Host response modulation
  - Immunogobulins/convalescent plasma
  - Glucocorticoids
  - Kinase inhibitors

SARS: Systematic Review of Treatment Effects

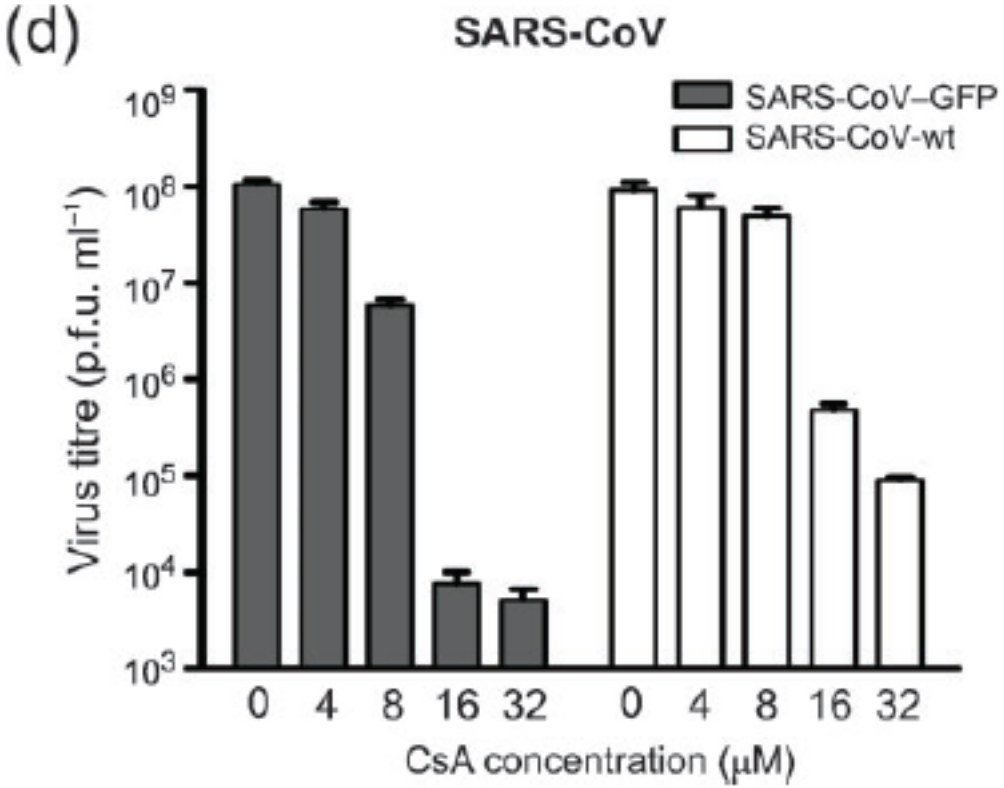
Lauren J. Stockman[1,2*], Richard Bellamy[3], Paul Garner[4]

Treatment	Inconclusive[a]	Possible Harm[a]	Total Studies with Evidence (English and Chinese)[b]
Ribavirin	26	4	30
Corticosteroid	25	4	29
LPV/r	2	0	2
IFN-α	3	0	3
Convalescent plasma or Immunoglobulin	7	0	7

[a]Studies were classified into six categories, but there were four categories without any studies: "possible benefit," "possible harm," "definite benefit," "definite harm" (see Box 1).
[b]Studies totalled 54; some reported on more than one drug.

Cyclosporin A inhibits the replication of diverse coronaviruses

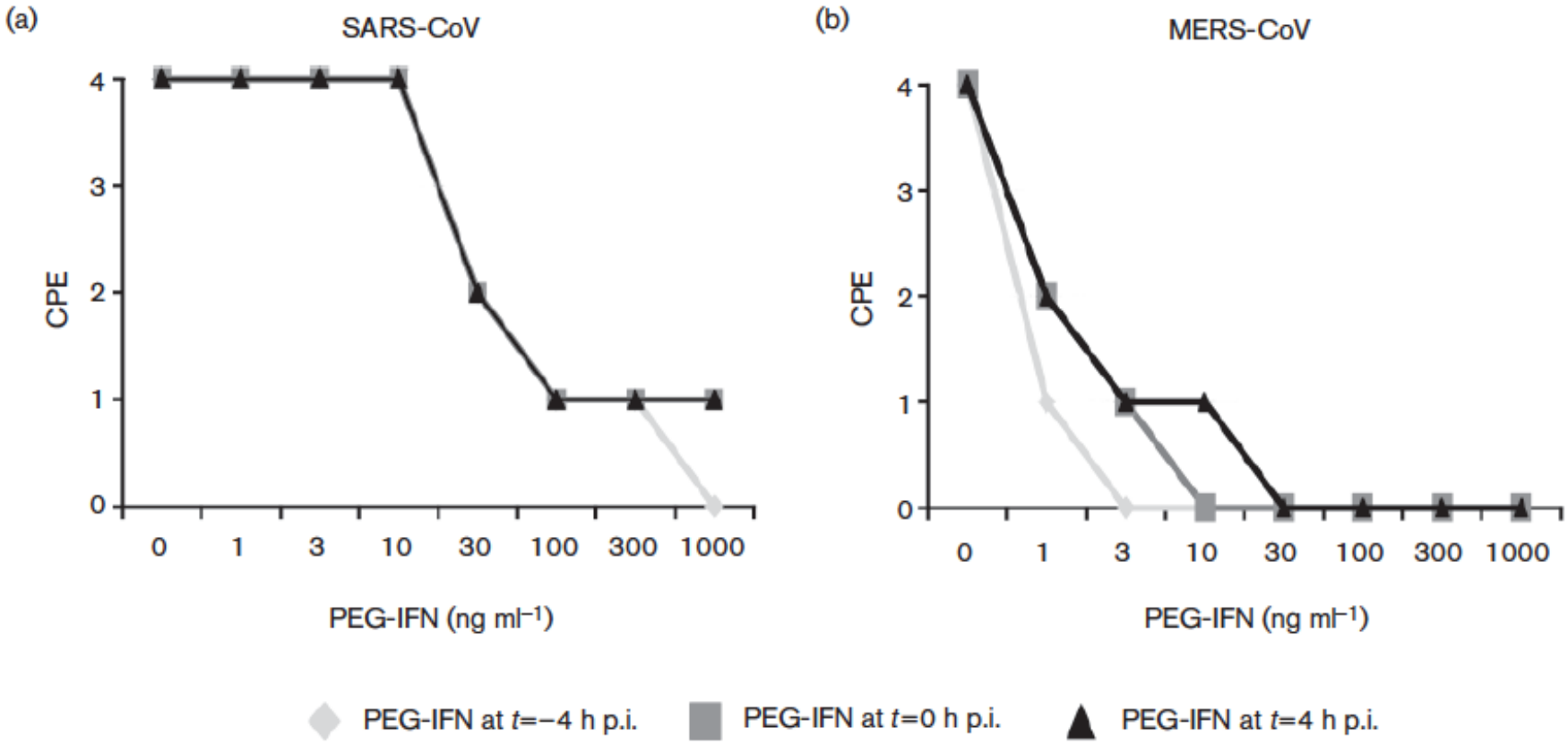
Adriaan H. de Wilde,[1] Jessika C. Zevenhoven-Dobbe,[1] Yvonne van der Meer,[1] Volker Thiel,[2,3] Krishna Narayanan,[4] Shinji Makino,[4] Eric J. Snijder[1] and Martijn J. van Hemert[1]



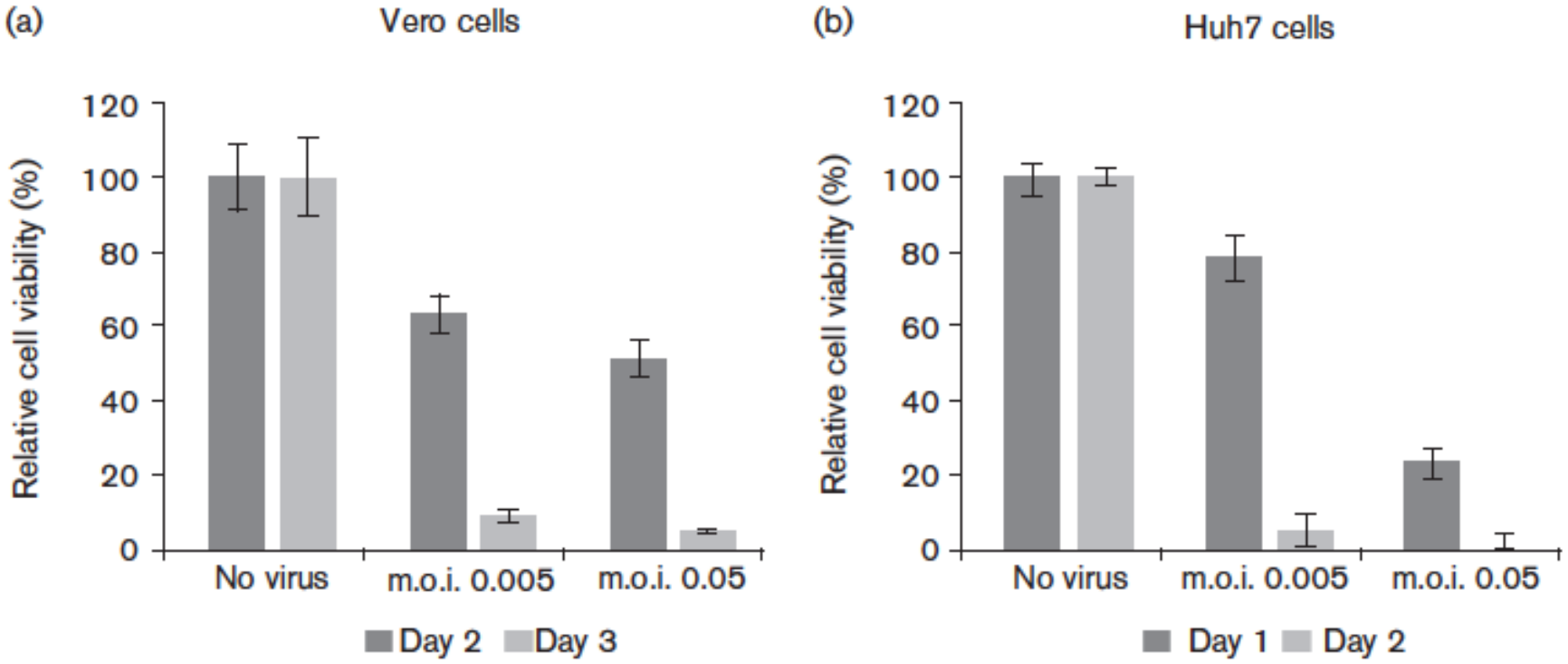
Journal of General Virology (2011), **92**, 2542–2548

MERS-coronavirus replication induces severe *in vitro* cytopathology and is strongly inhibited by cyclosporin A or interferon-α treatment

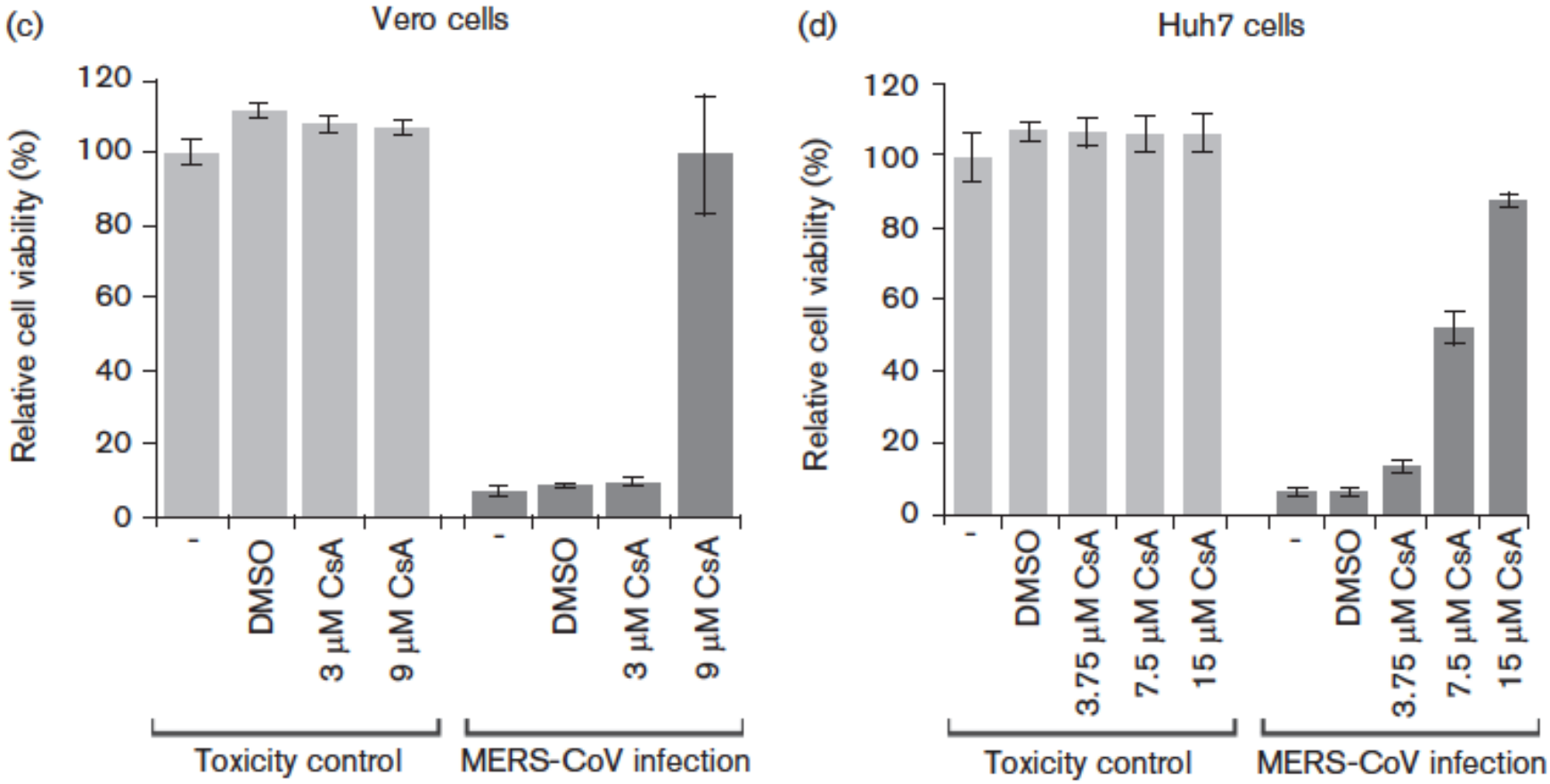
Adriaan H. de Wilde,[1] V. Stalin Raj,[2] Diede Oudshoorn,[1]
Theo M. Bestebroer,[2] Stefan van Nieuwkoop,[2] Ronald W. A. L. Limpens,[3]
Clara C. Posthuma,[1] Yvonne van der Meer,[1] Montserrat Bárcena,[3]
Bart L. Haagmans,[2] Eric J. Snijder[1] and Bernadette G. van den Hoogen[2]



Journal of General Virology (2013), **94**, 1749–1760



Journal of General Virology (2013), **94**, 1749–1760



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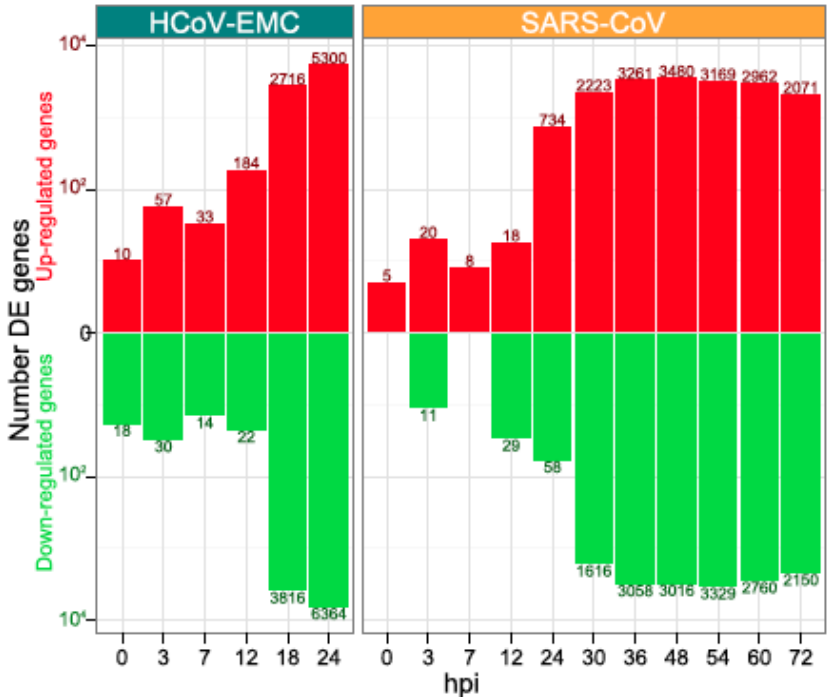
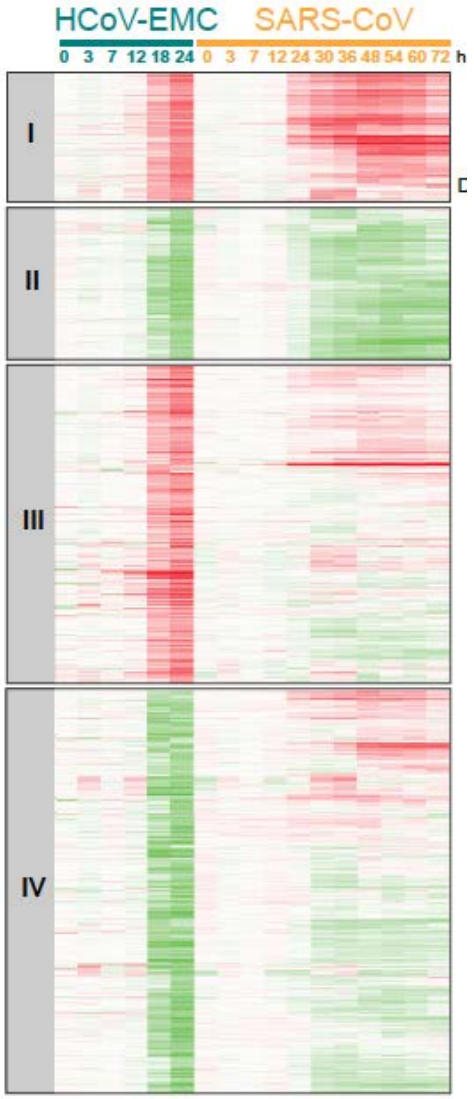
- ✓ Cyclosporin A is an inhibitor of HCoV-EMC replication in cell culture.
- ✓ HCoV-EMC was found to be 50-100 times more sensitive to interferon-alpha (IFN-**α**) treatment than SARS-CoV
- ✓ Important implications for the treatment of HCoV-EMC-infected patients.

Journal of General Virology (2013), **94**, 1749–1760

Cell Host Response to Infection with Novel Human Coronavirus EMC Predicts Potential Antivirals and Important Differences with SARS Coronavirus

Laurence Josset,[a] Vineet D. Menachery,[b,c] Lisa E. Gralinski,[b,c] Sudhakar Agnihothram,[b,c] Pavel Sova,[a] Victoria S. Carter,[a] Boyd L. Yount,[b,c] Rachel L. Graham,[b,c] Ralph S. Baric,[b,c] Michael G. Katze[a]





- ✓ HCoV-EMC infection, with 6,532 DE genes at 18 hpi and 11,664 genes at 24 hpi
- ✓ SARS-CoV induced changes of only 792 genes at 24 hpi with maximum changes at 48 and 54 hpi of 6,496 and 6,498 genes,

- ✓ HCoVEMC induced drastic changes in the host transcriptome with 12,392 DE genes at 18 hpi and/or 24 hpi

May/June 2013 Volume 4 Issue 3 e00165-13

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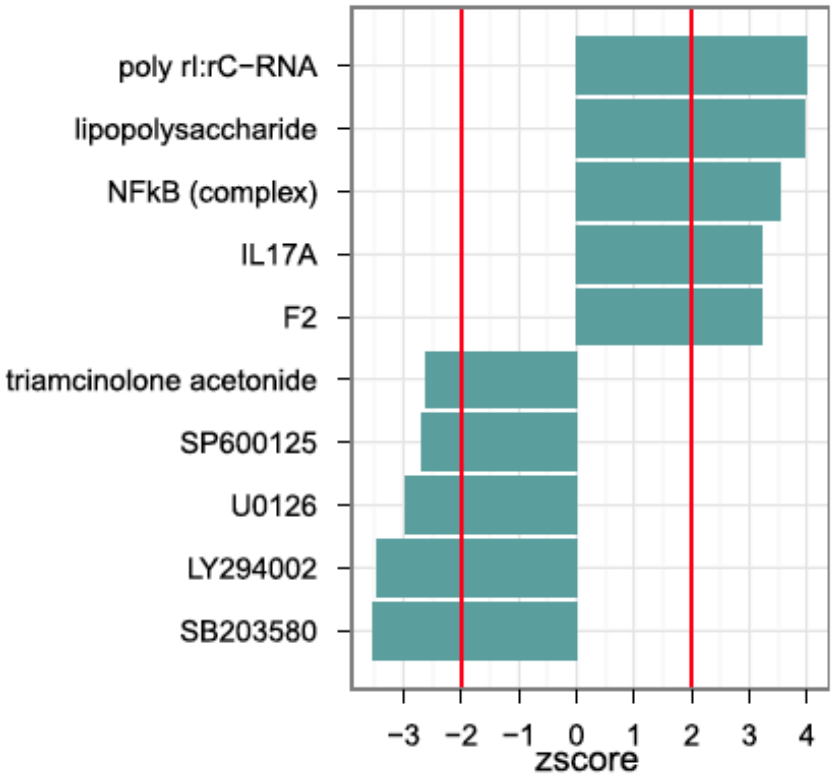

- ✓ Top 5 activated upstream regulators and top 5 inhibited upstream regulators of the early signature.
- ✓ The prediction of activation state is based on the global direction of changes of the 207 genes throughout infection with HCoV-EMC.
- ✓ Red lines depict the limit of significance

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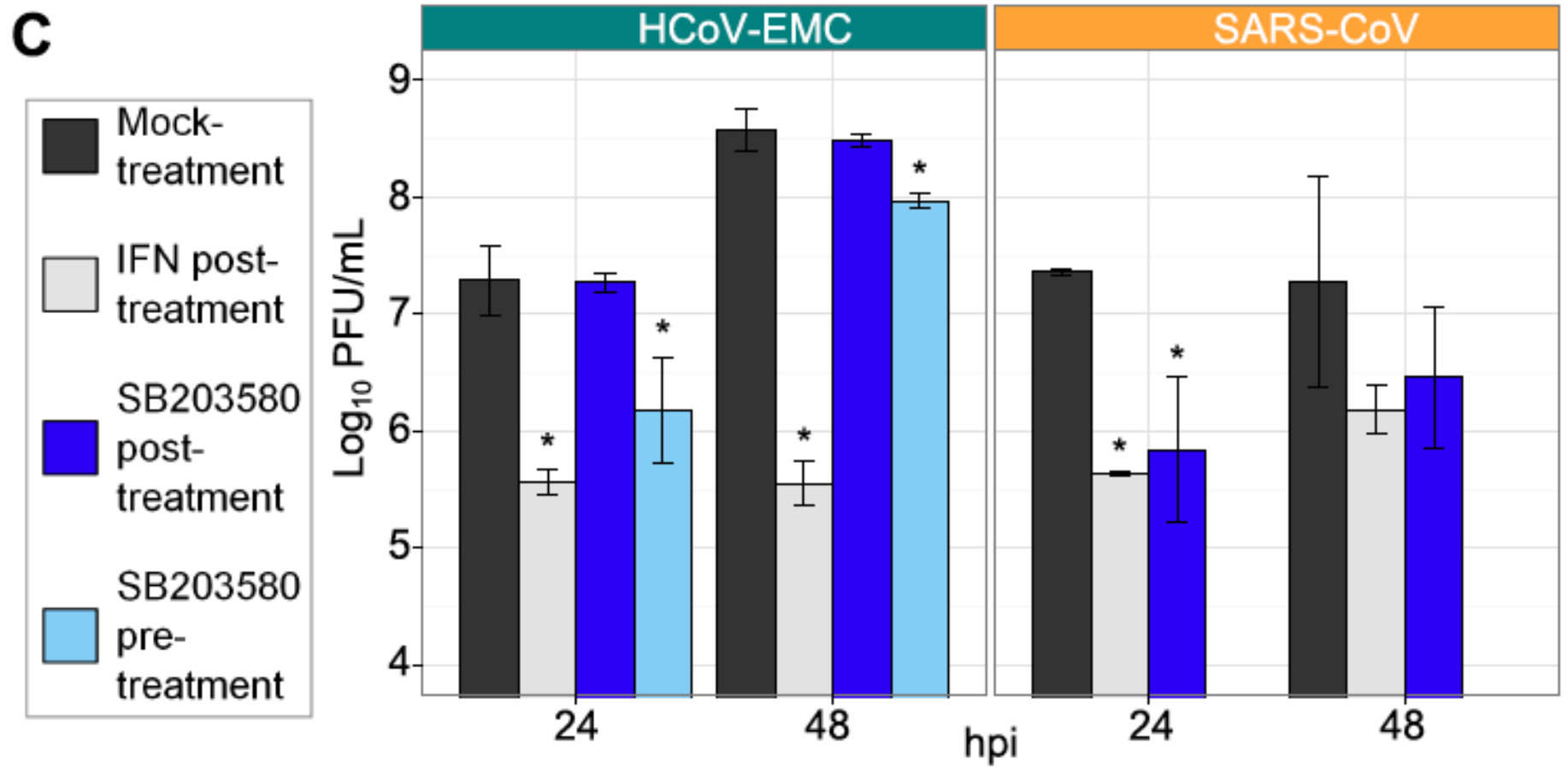
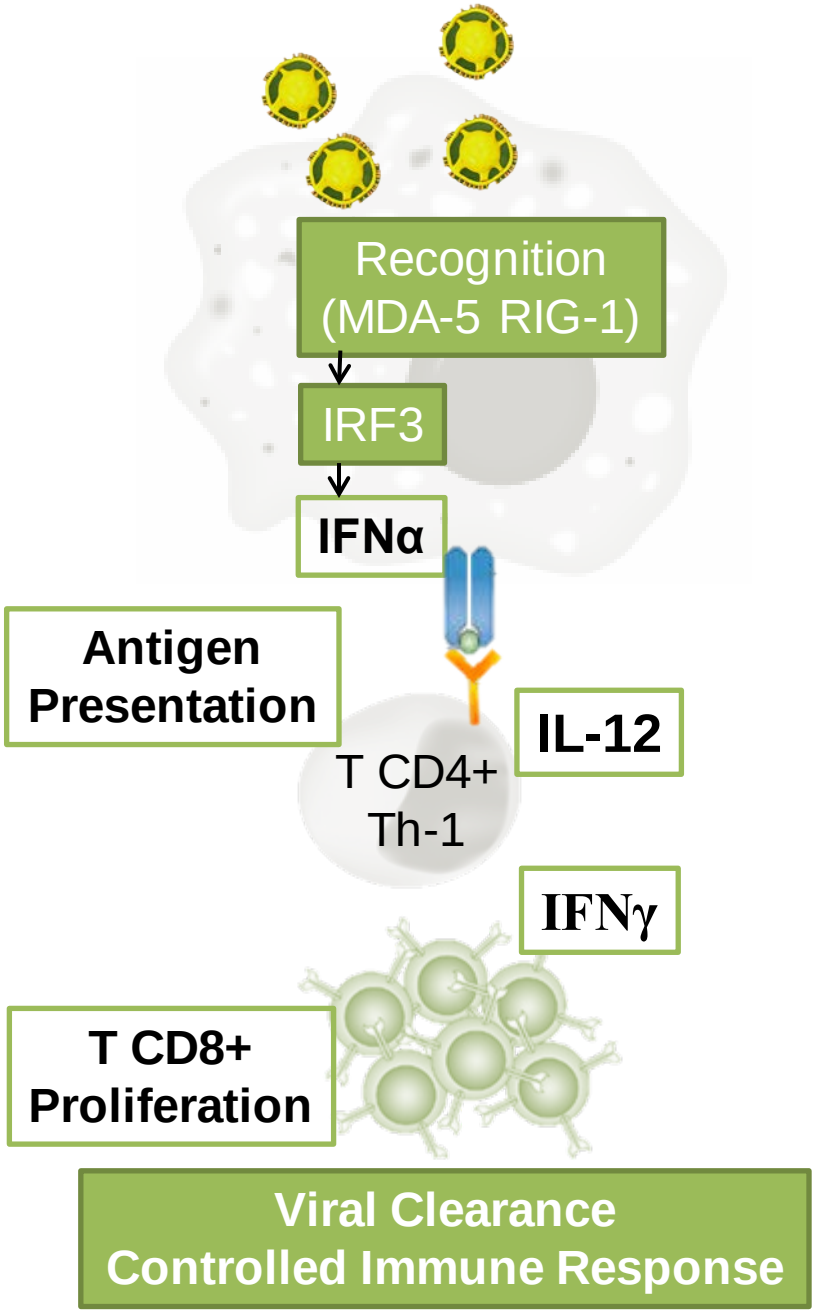


SB203580, an inhibitor of p38 MAPK,


Recognition
(MDA-5 RIG-1)
IRF3
IFNα
Antigen
Presentation
IL-12
T CD4+
Th-1
IFNγ
T CD8+
Proliferation
Viral Clearance
Controlled Immune Response

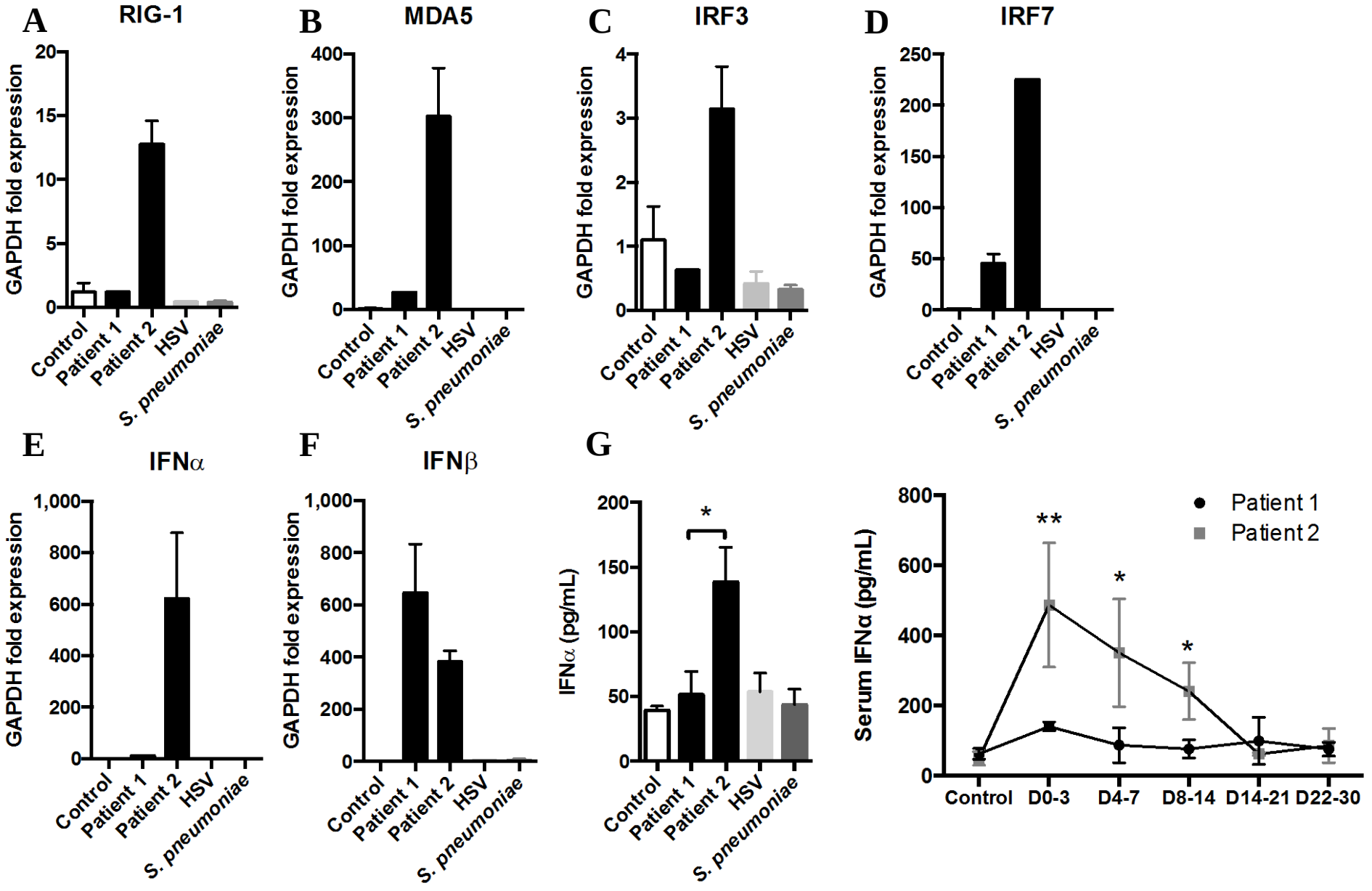
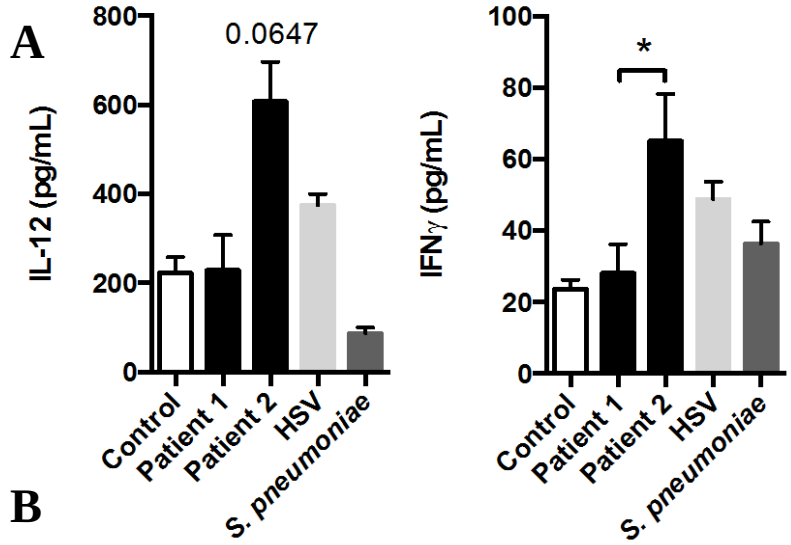
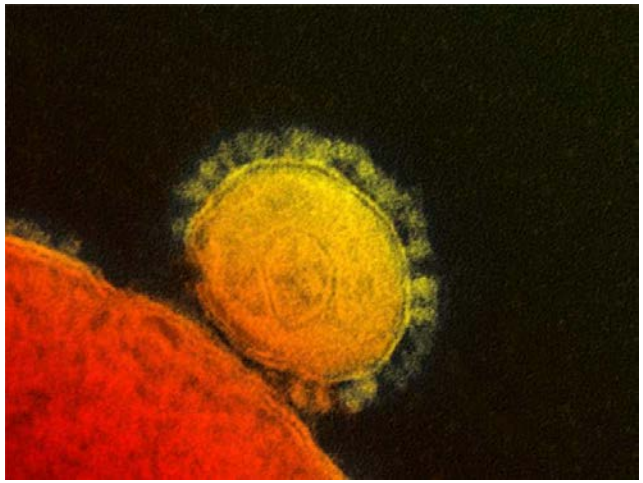
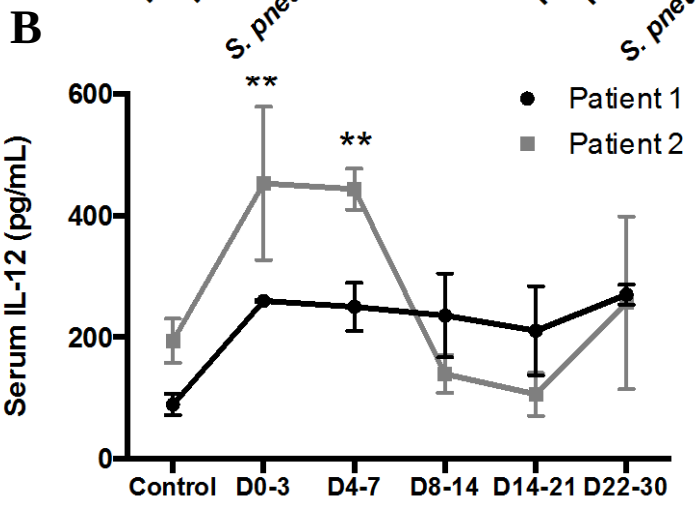
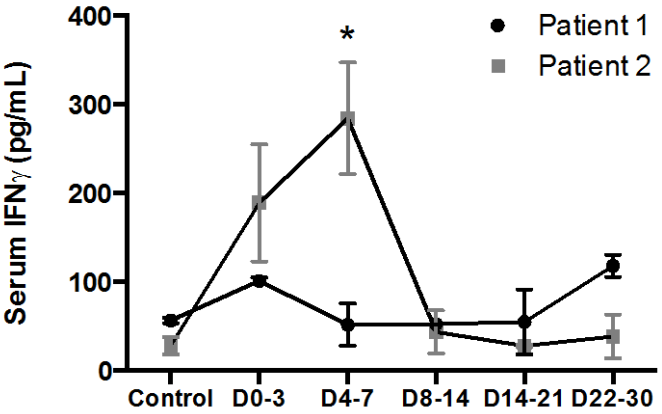

A
RIG-1
B
MDA5
C
IRF3
D
IRF7
GAPDH fold expression
Control
Patient 1
Patient 2
HSV
S. pneumoniae
E
IFNα
F
IFNβ
G
IFNα (pg/mL)
*
Serum IFNα (pg/mL)
**
Patient 1
Patient 2
Control
D0-3
D4-7
D8-14
D14-21
D22-30

Figure 1


A
0.0647
IL-12 (pg/mL)
800
600
400
200
0
Control
Patient 1
Patient 2
HSV
S. pneumoniae
*
IFNγ (pg/mL)
100
80
60
40
20
0




B
**
**
Patient 1
Patient 2
Serum IL-12 (pg/mL)
600
400
200
0
Control
D0-3
D4-7
D8-14
D14-21
D22-30


*
Patient 1
Patient 2
Serum IFNγ (pg/mL)
400
300
200
100
0
Control
D0-3
D4-7
D8-14
D14-21
D22-30

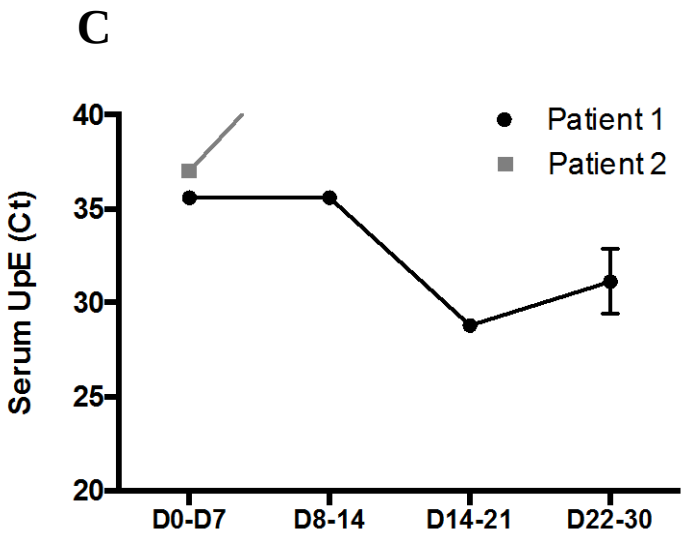
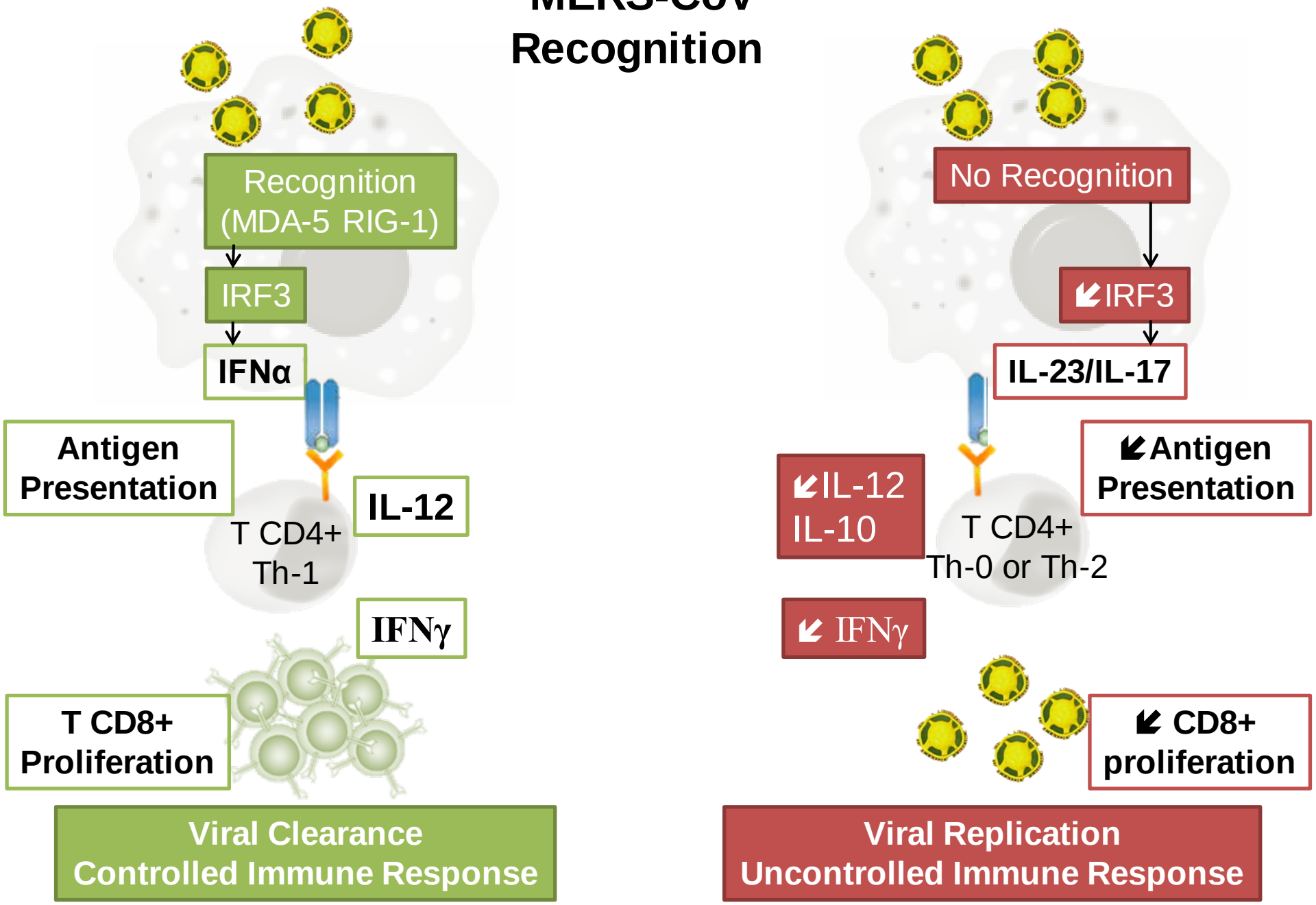

C
Patient 1
Patient 2
Serum UpE (Ct)
40
35
30
25
20
D0-D7
D8-14
D14-21
D22-30

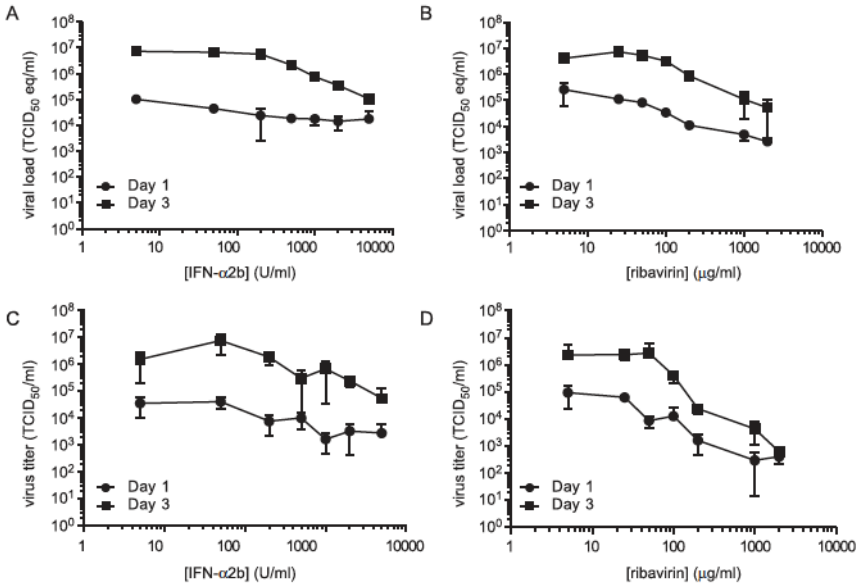
Figure 2

MERS-CoV Recognition

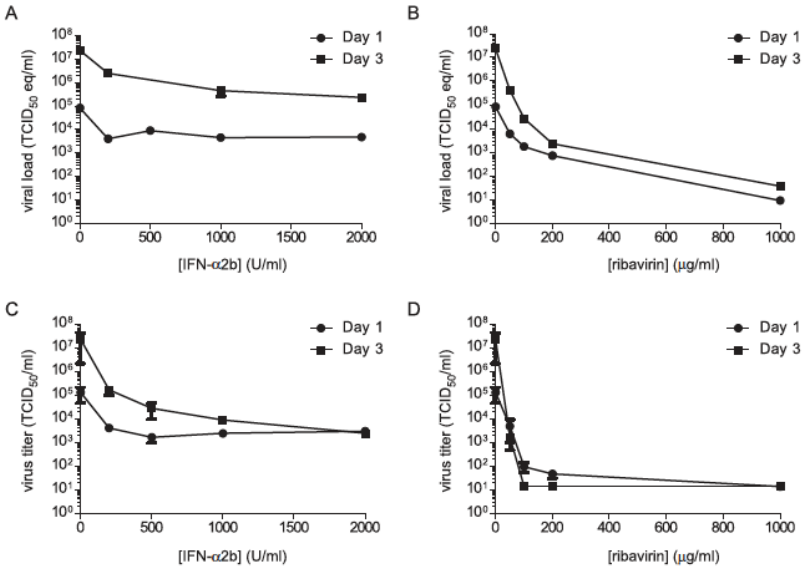


Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin

Darryl Falzarano[1], Emmie de Wit[1], Cynthia Martellaro[1], Julie Callison[1], Vincent J. Munster[2] & Heinz Feldmann[1,3]



Vero cells



LLC-MK2 cells

SCIENTIFIC REPORTS | 3 : 1686 | DOI: 10.1038/srep01686

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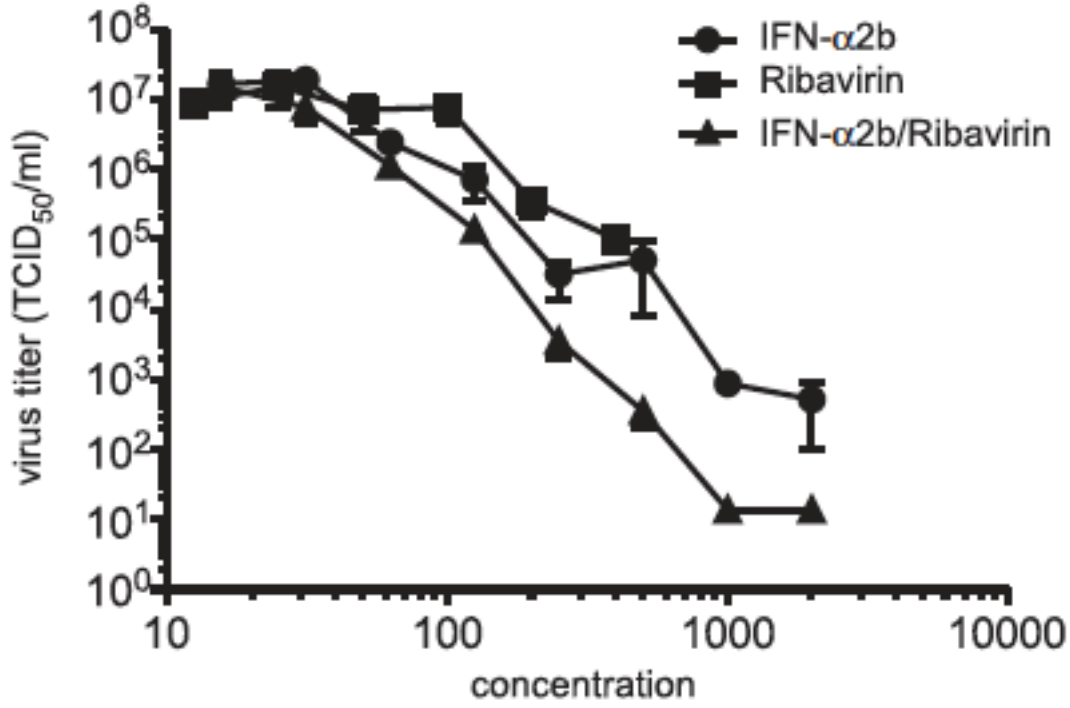
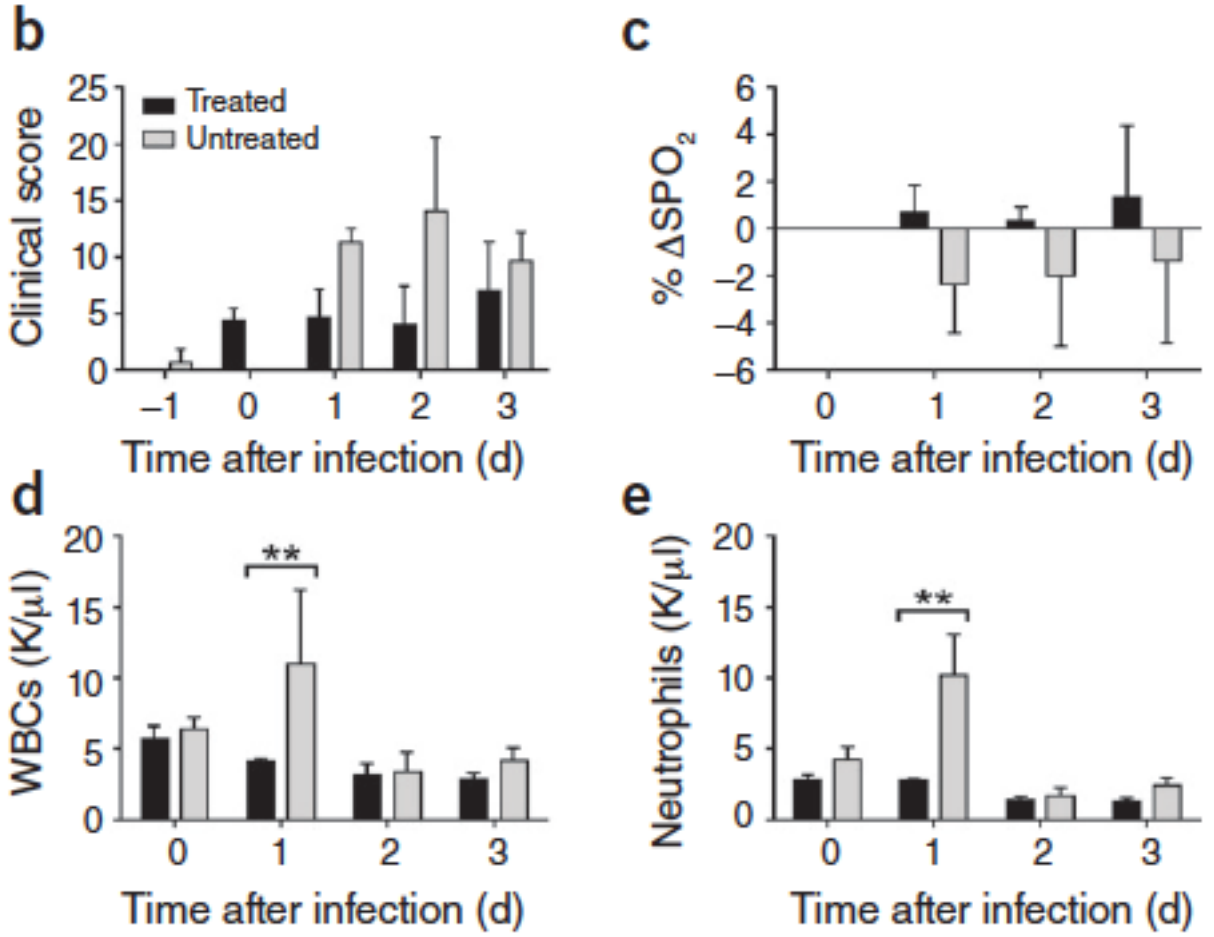


Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV–infected rhesus macaques

Darryl Falzarano[1], Emmie de Wit[1], Angela L Rasmussen[2], Friederike Feldmann[3], Atsushi Okumura[2], Dana P Scott[3], Doug Brining[3], Trenton Bushmaker[4], Cynthia Martellaro[1], Laura Baseler[1,5], Arndt G Benecke[2,6], Michael G Katze[2,7], Vincent J Munster[4] & Heinz Feldmann[1,8]



Received 24 May; accepted 27 August; published online 8 September 2013; doi:10.1038/nm.3362

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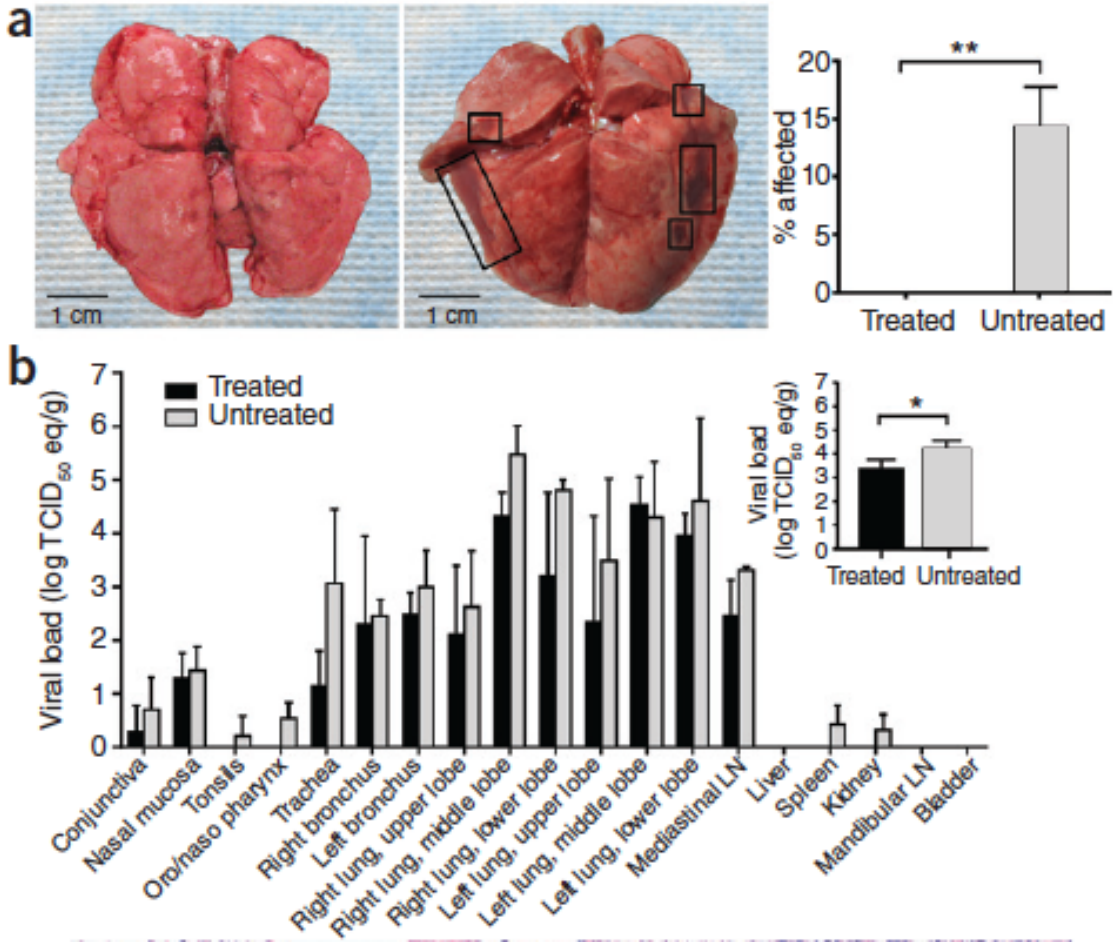
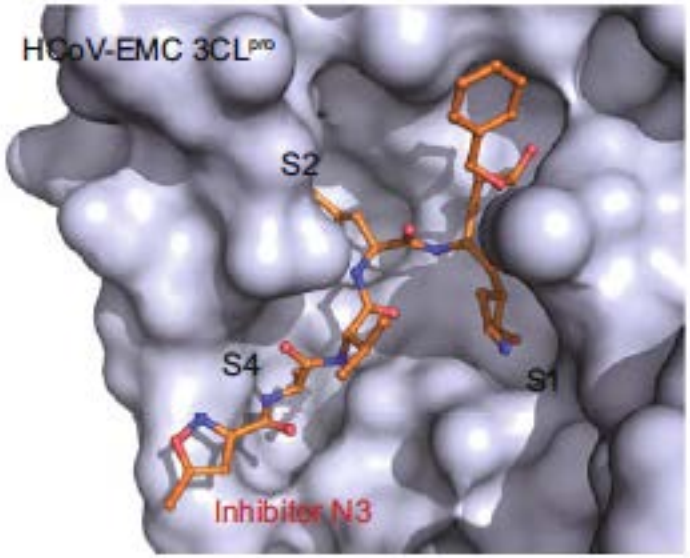


Received 24 May; accepted 27 August; published online 8 September 2013; doi:10.1038/nm.3362

The newly emerged SARS-Like coronavirus HCoV-EMC also has an "Achilles' heel": current effective inhibitor targeting a 3C-like protease

Zhilin Ren[1,2*], Liming Yan[1*], Ning Zhang[4], Yu Guo[2], Cheng Yang[2,4], Zhiyong Lou[1], Zihe Rao[1,2,3,4]✉

- ✓ Replication of coronavirus requires correct proteolytic processing of the **replicase polyprotein** by viral proteases, in particular a chymotrypsin-like protease **(3CLpro, also known as main protease Mpro**).
- ✓ Since 3CLpro is unique in the virus **but not found in the host cell**, this protein is a prominent target for the development antivirals against CoV infections
- ✓ Number of **inhibitors** have been discovered that prohibit the infection of CoV through their action on 3CLpro



Protein Cell 2013, 4(4): 248–250

Cross-reactive antibodies in convalescent SARS patients' sera against the emerging novel human coronavirus EMC (2012) by both immunofluorescent and neutralizing antibody tests

Kwok-Hung Chan [a,f], Jasper Fuk-Woo Chan [a,f], Herman Tse [a,b,c,d], Honglin Chen [a,b,c,d], Candy Choi-Yi Lau [a], Jian-Piao Cai [a], Alan Ka-Lun Tsang [a], Xincai Xiao [e], Kelvin Kai-Wang To [a,b,c,d], Susanna Kar-Pui Lau [a,b,c,d], Patrick Chiu-Yat Woo [a,b,c,d], Bo-Jiang Zheng [a,b,c,d], Ming Wang [e], Kwok-Yung Yuen [a,b,c,d,*]

- ✓ Seroprevalence study
  - ✓ 94 game-food animal handlers at a wild life market
  - ✓ 28 SARS patients
  - ✓ 152 healthy blood donors
- ✓ Two (2.1%) animal handlers had IF antibody titer of 1:20 against both HCoV-EMC and SARS-CoV with neutralizing antibody titer of <1:10.
- ✓ 17/28 (60.7%) of SARS patients had significant IF antibody titers with 7/28 (25%) having anti-HCoV-EMC neutralizing antibodies at low titers
- ✓ Virulence of SARS-CoV over other betacoronaviruses may boost cross-reactive neutralizing antibodies against other betacoronaviruses.
- ✓ Conclusions: Convalescent SARS sera may contain cross-reactive antibodies against other betacoronaviruses and confound seroprevalence study for HCoV-EMC.

Journal of Infection (2013) xx, 1–11

Therapeutic Options for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) – possible lessons from a systematic review of SARS-CoV therapy

Hisham Momattin [a], Khurram Mohammed [a], Alimuddin Zumla [b], Ziad A. Memish [c], Jaffar A. Al-Tawfiq [d,*]

Medication	Normal dose Crc I> 50ml/min	Impaired renal function Crcl (20-50 ml/min)	ESRD (Hemodialysis) CrCl< 20ml/min
Ribavirin oral	2000 mg loading dose then 1200mg q8h for 4 days, then 600mg po q8h for 4-6 days	2000 mg loading dose then 600 mg po q8h for 4 days, 200 mg po q6h for 4-6 days	2000 mg loading dose then 200mg po q6h for 4 days, then 200mg po q12h
Peg interferon alfa 2b	1.5mcg/kg once per week x 2	Same dose	Same dose
Lopinavir 400 mg/ ritonavir 100 mg oral	Lopinavir 400 mg/ ritonavir 100 mg twice daily for 10 days. May be given in combination with Ribavirin	Same dose	Same dose
convalescent plasma	300- 500 ml of full plasma (3 – 5 ml/kg) With a rate of 2ml/min for one time in day 2 of ICU admission.	Same dose	Same dose

Propositions

- ✓ Compare Ribavirin+IFN vs either Riba or **IFN alone**
  - Ribavirin 10mg/kg/8h IV
  - IFN α2b 5 M IU/kg/16h SC or PEG-IFN
- ✓ Monoclonal antibodies: Dutch and English
- ✓ **Convalescent plasma** if available
- ✓ Consider may be steroids very early in the disease as well as cyclosporin
  - based on the host response profile
  - Associated to IFN for replication?