Hepatitis C Virus
SARS-Co Virus

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Viral Hepatitis - Historical Perspective

“Infectious”

Viral hepatitis

“Serum”

E  Enterically transmitted

A

B  C  D

NANB

F, G, ? other

Parenterally transmitted
HEPATITIS C VIRUS
An Emerging Global Pathogen

- Identified in 1989: Immunoscreening an expression library with serum from a patient with post-transfusion non-A, non-B hepatitis
- HCV epidemic – Five times higher prevalence than AIDS
- WHO estimates 3% world population
- ~200 million people
HCV: Epidemiology

- 35,000-180,000 acute infections in U.S./year
- 3-4 million infected in U.S.
- 20-30% of those with HIV also have HCV
Sources of Infection for Persons With Hepatitis C

- Injecting drug use: 60%
- Sexual: 15%
- Transfusion (before screening): 10%
- Occupational: 4%
- Other: 1%*
- Unknown: 10%

* Nosocomial; iatrogenic; perinatal

Source: Sentinel Counties, CDC

Source: Centers for Disease Control and Prevention
Impact of The Disease

Clinical Consequences

- Chronic hepatitis
- Cirrhosis
- Hepatic fibrosis
- Hepatocellular carcinoma
- Extrahepatic manifestations
- End-stage liver disease necessitating liver transplantation
Hepatitis C Virus-the Silent Killer
HCV: Natural History

Acute HCV
- 80%

Chronic HCV
- 20%
  - 20%
  - 80%
    - Age, Sex, race
    - Alcohol, diabetes, Obesity
    - Co-infection (HBV, HIV)

Resolution
- Immune response
- Host factors
- Early Tx

Cirrhosis
- 20%

Stable Infection
- 80%

HCC
- 1-4% / year

~20 years
CURRENT HCV THERAPIES

• No Vaccines
• Approved therapies include
  1st generation: IFN-α, IFN-α + Ribavirin
  2nd generation: PEG-IFN-α, PEG-IFN-α + Ribavirin
  ▪ Remarkable increase in response to current antiviral drugs
    (~50% with genotype 1, ~80% other genotypes)

Drawbacks

▪ Severe side effects severe leading to patient non-compliance
▪ Cost of therapy
▪ Emergence of viral quasispecies in infected individuals
Therapies in Development

Antifibrotics

Building a Better IFN

RBV Analogs

Protease/Polymerase Inhibitors

Immunomodulators

Regulation of IFN Response Genes

Apoptosis Regulators
<table>
<thead>
<tr>
<th>Genus/species</th>
<th>Virus name abbreviation</th>
<th>Usual host(s)</th>
<th>Transmission</th>
<th>Disease</th>
<th>World distribution</th>
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<tbody>
<tr>
<td><strong>Flavivirus</strong></td>
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<tr>
<td>Dengue (Types 1-4)</td>
<td>DENV</td>
<td>Humans</td>
<td>Mosquito-borne</td>
<td>Dengue fever, shock, hemorrhage</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>YFV</td>
<td>Primates&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mosquito-borne</td>
<td>Hemorrhage, liver destruction</td>
<td>Africa, Americas</td>
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<tr>
<td>Japanese encephalitis</td>
<td>JEV</td>
<td>Mammals, especially swine</td>
<td>Mosquito-borne</td>
<td>Encephalitis</td>
<td>Widespread in Asia</td>
</tr>
<tr>
<td>St. Louis encephalitis</td>
<td>SLEV</td>
<td>Mammals, birds</td>
<td>Mosquito-borne</td>
<td>Encephalitis</td>
<td>North America</td>
</tr>
<tr>
<td>Murray Valley encephalitis</td>
<td>MVEV</td>
<td>Mammals, birds</td>
<td>Mosquito-borne</td>
<td>Encephalitis</td>
<td>Australia</td>
</tr>
<tr>
<td>Tick-borne encephalitis</td>
<td>TBEV</td>
<td>Mammals&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Tick-borne</td>
<td>Encephalitis</td>
<td>Europe, Asia</td>
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<tr>
<td>West Nile</td>
<td>WNV</td>
<td>Mammals, birds</td>
<td>Mosquito-borne</td>
<td>Encephalitis</td>
<td>Europe, Africa, North America</td>
</tr>
<tr>
<td><strong>Hepacivirus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>HCV</td>
<td>Humans</td>
<td>Parenteral, transfusion</td>
<td>Hepatitis, liver cancer</td>
<td>Worldwide</td>
</tr>
<tr>
<td><strong>Pestivirus</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Classical swine fever</td>
<td>CSFV</td>
<td>Swine</td>
<td>Contact</td>
<td>Fever, acute gastroenteritis</td>
<td>Europe, Americas</td>
</tr>
<tr>
<td>Bovine viral diarrhea</td>
<td>BVDV</td>
<td>Cattle</td>
<td>Contact</td>
<td>Usually none&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Worldwide</td>
</tr>
</tbody>
</table>

<sup>a</sup> Including humans.

<sup>b</sup> Calves infected in utero develop persistent infections that can lead to mucosal disease.
HCV: Classification

- Enveloped RNA virus
- Genus Hepacivirus
- Family Flaviviridae, with classical flaviviruses and animal pestiviruses
- 6 genotypes worldwide, many subtypes and isolates based on nucleotide diversity
- Quasispecies within individual
Distribution of Hepatitis C Genotypes
Genetic Organization and Polyprotein Processing of HCV
Structures and Membrane Association of HCV proteins
LIFE CYCLE of HCV
Current Models for HCV Entry

NATURE REVIEWS 2007: 5
Systems for the Study of HCV Replication, Entry, and Infectivity

Journal of Virology, 2007: 81
HCV Replicon Systems
HCV “Membraneous Web” associated Replication Complex
Cellular cofactors affecting hepatitis C virus infection and replication

Glenn Randall\textsuperscript{a,b}, Maryline Panis\textsuperscript{a}, Jacob D. Cooper\textsuperscript{b}, Timothy L. Tellinghuisen\textsuperscript{a,c}, Karen E. Sukhodolets\textsuperscript{d}, Sebastien Pfeffer\textsuperscript{e,f}, Markus Landthaler\textsuperscript{e}, Pablo Landgraf\textsuperscript{e}, Sherry Kan\textsuperscript{a}, Brett D. Lindenbach\textsuperscript{a}, Minchen Chien\textsuperscript{g}, David B. Weiner\textsuperscript{h}, James J. Russo\textsuperscript{g}, Jingyue Ju\textsuperscript{g,h}, Michael J. Brownstein\textsuperscript{l}, Robert Sheridan\textsuperscript{l}, Chris Sander\textsuperscript{l}, Mihaela Zavolan\textsuperscript{k}, Thomas Tuschi\textsuperscript{e}, and Charles M. Rice\textsuperscript{a1}

\textsuperscript{a}Laboratory of Virology and Infectious Disease, Center for the Study of Hepatitis C, and \textsuperscript{b}Howard Hughes Medical Institute, Laboratory of RNA Molecular Biology, The Rockefeller University, New York, NY 10021; \textsuperscript{c}Department of Microbiology, University of Chicago, Chicago, IL 60637; \textsuperscript{d}Columbia Genome Center, New York, NY 10032; \textsuperscript{e}Department of Chemical Engineering, Columbia University, New York, NY 10027; \textsuperscript{f}J. Craig Venter Institute, Rockville, MD 20850; \textsuperscript{g}Computational Biology Center, Memorial Sloan-Kettering Cancer Center, New York, NY 10021; and \textsuperscript{h}Biozentrum, Universität Basel, CH 4056 Basel, Switzerland; and \textsuperscript{i}Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, MO 63110
Table 1. Changes in HCV replication after siRNA targeting of host gene RNAs

<table>
<thead>
<tr>
<th>siRNA*</th>
<th>Virus$^1$</th>
<th>HCV RNA</th>
<th>siRNA</th>
<th>HCV RNA</th>
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<tbody>
<tr>
<td>HCV</td>
<td>$&lt; -230$</td>
<td>$&lt; -10000$</td>
<td>MAPK12</td>
<td>$-2.0 \pm 0.5^*$</td>
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<tr>
<td>DDX3X</td>
<td>$-42 \pm 19^*$</td>
<td>$-1600 \pm 800$</td>
<td>NCL</td>
<td>$-1.8 \pm 0.4^*$</td>
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<tr>
<td>EIF253</td>
<td>$-30 \pm 3.7^*$</td>
<td>$-55 \pm 34$</td>
<td>CDC2</td>
<td>$-1.8 \pm 0.5^*$</td>
</tr>
<tr>
<td>STAT3</td>
<td>$-13 \pm 4.4^*$</td>
<td>$-8.3 \pm 2.4$</td>
<td>EIF2AK3</td>
<td>$-1.8 \pm 0.4^*$</td>
</tr>
<tr>
<td>CD81</td>
<td>$-11 \pm 0.6^*$</td>
<td>$-6.1 \pm 2.6$</td>
<td>IPO4</td>
<td>$-1.7^*$</td>
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<td>ELAVL1</td>
<td>$-9.1 \pm 2.8^*$</td>
<td>$-3.3 \pm 0.4$</td>
<td>HNRPL</td>
<td>$-1.5 \pm 1.8^*$</td>
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<tr>
<td>VAP-A8C$^*$</td>
<td>$-8.7 \pm 1.7^*$</td>
<td>$-5.9 \pm 0.3$</td>
<td>XBP1</td>
<td>$-1.4 \pm 1.8^*$</td>
</tr>
<tr>
<td>Dicer1</td>
<td>$-7.5 \pm 2.5^*$</td>
<td>$-3.1 \pm 0.7$</td>
<td>CSNK2A1</td>
<td>$-1.3 \pm 0.1^*$</td>
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<tr>
<td>HSPBP1</td>
<td>$-6.4 \pm 0.7^*$</td>
<td>$-5.7 \pm 2.3$</td>
<td>TP53</td>
<td>$-1.3^*$</td>
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<tr>
<td>GRB2</td>
<td>$-6.3 \pm 0.9^*$</td>
<td>$-1.3 \pm 0.3$</td>
<td>EIF2B3</td>
<td>$-1.2 \pm 0.1^*$</td>
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<tr>
<td>HM13</td>
<td>$-6.2 \pm 1.8^*$</td>
<td>$-10 \pm 4.0$</td>
<td>CALR</td>
<td>$-1.2 \pm 1.8^*$</td>
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<tr>
<td>RAF1</td>
<td>$-5.6 \pm 1.8^*$</td>
<td>$-3.6 \pm 3.1$</td>
<td>SCD</td>
<td>$-1.2 \pm 2.3^*$</td>
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<tr>
<td>EIF2AK2</td>
<td>$-5.5 \pm 0.7^*$</td>
<td>$-1.9 \pm 0.7$</td>
<td>VPS4A</td>
<td>$-1.1 \pm 1.3^*$</td>
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<td>PSMA7</td>
<td>$-5.4 \pm 1.7^*$</td>
<td>$-1.3 \pm 0.8$</td>
<td>AKT1</td>
<td>$1.0 \pm 0.1^*$</td>
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<tr>
<td>SRCAP</td>
<td>$-4.0 \pm 1.4^*$</td>
<td>$-1.1 \pm 0.4$</td>
<td>SRR</td>
<td>$1.0 \pm 0.2^*$</td>
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<tr>
<td>PTBP1</td>
<td>$-4.7 \pm 1.6^*$</td>
<td>$-2.1 \pm 1.0$</td>
<td>CDK2</td>
<td>$1.1 \pm 0.5^*$</td>
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<tr>
<td>GAPDH</td>
<td>$-4.6 \pm 0.5^*$</td>
<td>$-2.2 \pm 0.3$</td>
<td>ISG15</td>
<td>$1.1 \pm 0.2^*$</td>
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<tr>
<td>EIF4E</td>
<td>$-4.4 \pm 0.8^*$</td>
<td>$3.6 \pm 1.3$</td>
<td>SCAR1</td>
<td>$1.1^*$</td>
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<td>VPS35</td>
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<td>$-2.3 \pm 0.4$</td>
<td>USP18</td>
<td>$1.1 \pm 0.2^*$</td>
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<tr>
<td>RANBP5</td>
<td>$-4.4 \pm 1.1^*$</td>
<td>$-4.1 \pm 0.8$</td>
<td>PRMT1</td>
<td>$1.2 \pm 0.6^*$</td>
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<tr>
<td>HNRPCA</td>
<td>$-3.9 \pm 0.9^*$</td>
<td>$-3.0 \pm 0.2$</td>
<td>PCBP1</td>
<td>$1.2 \pm 0.6^*$</td>
</tr>
<tr>
<td>ACTN1</td>
<td>$-3.9 \pm 0.7^*$</td>
<td>$-4.0 \pm 1.6$</td>
<td>RPL3</td>
<td>$1.3 \pm 0.0$</td>
</tr>
<tr>
<td>RELA</td>
<td>$-3.4 \pm 0.8^*$</td>
<td>$-3.5 \pm 0.7$</td>
<td>PRMT5</td>
<td>$1.3 \pm 0.0^*$</td>
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<tr>
<td>MAPK1</td>
<td>$-3.2^*$</td>
<td>$2.0 \pm 0.8$</td>
<td>LSM1</td>
<td>$1.3 \pm 0.6^*$</td>
</tr>
<tr>
<td>PCBP2$^*$</td>
<td>$-3.1^<em>$, $3.4^</em>$</td>
<td>$-1.8, 1.8$</td>
<td>ISGF3G</td>
<td>$1.5^*$</td>
</tr>
<tr>
<td>RPL22</td>
<td>$-2.0 \pm 0.3^*$</td>
<td>$-6.4 \pm 0.3$</td>
<td>PRKACA</td>
<td>$1.5^*$</td>
</tr>
<tr>
<td>PDK1</td>
<td>$-2.8 \pm 0.6^*$</td>
<td>$-4.2 \pm 2.2$</td>
<td>DNAJC14</td>
<td>$1.5 \pm 1.1^*$</td>
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<tr>
<td>AHS1</td>
<td>$-2.5 \pm 0.5^*$</td>
<td>$-3.2 \pm 1.0$</td>
<td>HSPCA</td>
<td>$1.7 \pm 0.4^*$</td>
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<tr>
<td>CDK8</td>
<td>$-2.4 \pm 1.0^*$</td>
<td>$2.1 \pm 1.2$</td>
<td>ADI1</td>
<td>$2.0 \pm 1.1^*$</td>
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<td>SEC11L1</td>
<td>$-2.4 \pm 0.4^*$</td>
<td>$-2.5 \pm 0.7$</td>
<td>SNX1</td>
<td>$2.4 \pm 1.3^*$</td>
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<tr>
<td>CANX</td>
<td>$-2.2 \pm 0.7^*$</td>
<td>$-1.4 \pm 0.1$</td>
<td>ATF6</td>
<td>$6.8^*$</td>
</tr>
</tbody>
</table>

Dots represent number of days between siRNA treatment and initial infection that produced the most extreme viral phenotype.

*Names refer to the gene name of the siRNA target (HUGO nomenclature).

Values represent fold change in HCV levels plus SEM in specific siRNA-treated cells compared with controls. Values are based on the geometric mean of two replicate experiments. A negative value reflects a decrease in relative HCV levels.

$^*$VAP-A8C siRNAs target VAPA, VAPB, and VAPC.

$^*$PCBP2 siRNAs produce an early increase in HCV levels, followed by a decrease.
HCV REPLICASE

66 kDa, 591 amino acids

• Viral RdRp
• Residues 2420-3010
• 66 kDa, 591 amino acids
• Cloned, expressed and purified in 1996
• Membrane associated Phosphoprotein
• C-terminal anchor sequence required for membrane localization and replication but not for enzymatic activity
• Forms oligomers, exhibits cooperativity in enzyme assays
Structural Organization of NS5B

COMPARISON OF POLYMERASE STRUCTURE AND SEQUENCE

NS5B INHIBITORS

Two Broad Classes

- Nucleoside (NI): act by competing with the natural ribonucleoside triphosphate substrates of NS5B at its catalytic center

- Non-Nucleoside (NNI): chemically diverse group of compounds, inhibit the initiation and or elongation step by binding near the active site or discrete allosteric sites

- Three distinct inhibitor binding sites have been located

- In drug discovery, knowledge of the inhibitor site of action is crucial to guiding Medicinal chemistry efforts

- Structural activity relationships are further complicated by the variation observed for each of the NNI binding sites between genotype and subtypes
NS5B INHIBITOR BINDING POCKET

Pauwels et al., JOURNAL OF VIROLOGY, 2007
CHEMICAL GENETICS APPROACH TO VIROLOGY

CYCLOSPORIN A

Target: Cyclophilin (CyP), the calcineurin (CN)-NF-AT pathway, P-glycoprotein (P-gp)

TAMOXIFEN

Target: ESR, P-glycoprotein, calmodulin, protein kinase C
Specific inhibition of hepatitis C virus replication by cyclosporin A

Mina Nakagawa,¹ Naoya Sakamoto,*,¹ Nobuyuki Enomoto,
Yoko Tanabe, Nobuhiko Kanazawa, Tomoyuki Koyama, Masayuki Kurosaki,
Shinya Maekawa, Tsuyoshi Yamashiro, Cheng-Hsin Chen, Yasuhiro Itsui,
Sei Kakinuma, and Mamoru Watanabe

Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

Received 7 November 2003
Cyclophilin B Is a Functional Regulator of Hepatitis C Virus RNA Polymerase

Koichi Watashi, Naoto Ishii, Makoto Hijikata,
Daisuke Inoue, Takayuki Murata, Yusuke Miyanari,
and Kunitada Shimotohno*
Laboratory of Human Tumor Viruses
Department of Viral Oncology
Institute for Virus Research
Kyoto University
Kyoto 606-8507
Japan

Summary

Viruses depend on host-derived factors for their efficient genome replication. Here, we demonstrate that a cellular peptidyl-prolyl cis-trans isomerase (PPlase), cyclophilin B (CyPB), is critical for the efficient replication of the hepatitis C virus (HCV) genome. CyPB interacted with the HCV RNA polymerase NS5B to directly stimulate its RNA binding activity. Both the RNA interference (RNAi)-mediated reduction of endogenous CyPB expression and the induced loss of NS5B binding to CyPB decreased the levels of HCV replication. Thus, CyPB functions as a stimulatory regulator of NS5B in HCV replication machinery. This regulation mechanism for viral replication identifies CyPB as a target for antiviral therapeutic strategies.
MODEL OF ROLE OF CYPB IN HCV REPLICATION
UNMASKING A NEW DISEASE
**Historical Perspective**

- In Nov 2002, first outbreak involving several hundred cases of atypical pneumonia of unknown etiology occurred in the Guangdong Province of People’s Republic of China.

- Within the next few months, similar cases were reported from Hong-Kong, Vietnam, Singapore and Canada.

- By Feb 2003, WHO issued a Global Alert for an illness designated as “Severe Acute Respiratory Syndrome (SARS)”.

- Co-ordination of International effort and collaboration of Clinicians, Researchers and Epidemiologist to control the spread of SARS.
The Worldwide Spread of SARS

Sars* worldwide
Number of reported deaths

Canada 22
China 235
Taiwan 18
Hong Kong 215
Thailand 2
Malaysia 2
Philippines 2
Vietnam 5
S. Africa 1
Singapore 28
Total 530

Sources: World Health Organisation; Local health authorities  * Severe Acute Respiratory Syndrome
Milestones

• First major breakthrough achieved in March 2003; Labs in US, Canada, Germany and Hong-Kong isolated a novel coronavirus from SARS patient and identified it as the etiological agent of the SARS outbreak.

• 14\textsuperscript{th} April 2003, next mile-stone achieved by the simultaneous decoding of the genomic sequence of two SARS-CoV isolates.

• ‘Tor-2 strain’ British Columbia Center for Disease Control in Vancouver, Canada.

• ‘Urbani strain’ CDC in Atlanta, Departments of Virology at Erasmus University in The Netherlands and Bernhard-Nocht Institute Germany.

• SARS-CoV: “The First New Virus of the 21st Century”
The Genome Sequence of the SARS-Associated Coronavirus

Marco A. Marra,1,* Steven J. M. Jones,1 Caroline R. Astell,1 Robert A. Holt,1 Angela Brooks-Wilson,1 Yaron S. N. Butterfield,1 Jaswinder Khattria,1 Jennifer K. Asano,1 Sarah A. Barber,1 Susanna Y. Chan,1 Alison Cloutier,1 Shaun M. Coughlin,1 Doug Freeman,1 Noreen Girm,1 Obi L. Griffith,1 Stephen R. Leach,1 Michael Mayo,1 Helen McDonald,1 Stephen B. Montgomery,1 Pawan K. Pandoh,1 Anca S. Petrescu,1 A. Gordon Robertson,1 Jacqueline E. Schein,1 Asim Siddiqui,1 Duane E. Smailus,1 Jeff M. Stott,1 George S. Yang1

Francis Plummer,2 Anton Andonov,2 Harvey Artsob,2 Nathalie Bastien,2 Kathy Bernard,2 Timothy F. Booth,2 Donnie Bowness,2 Michael Drebot,2 Lisa Fernando,2 Ramon Flick,2 Michael Garbutt,2 Michael Gray,2 Allen Grolla,2 Steven Jones,2 Heinz Feldmann,2 Adrienne Meyers,2 Amin Kabani,2 Yan Li,2 Susan Normand,2 Ute Stroher,2 Graham A. Tipples,2 Shaun Tyler,2 Robert Vogrig,2 Diane Ward,2 Bryan Watson2

Robert C. Brunham,3 Mel Krajden,3 Martin Petric,3 Danuta M. Skowronski3

Chris Upton,4 Rachel L. Roper4

1British Columbia Cancer Agency Genome Sciences Centre, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6, Canada. 2National Microbiology Laboratory, 1015 Arlington Street, Winnipeg, Manitoba R3E 3R2, Canada. 3British Columbia Centre for Disease Control and University of British Columbia Centre for Disease Control, 655 West 12th Avenue, Vancouver, British Columbia V5Z 4R4, Canada. 4Department of Biochemistry and Microbiology, University of Victoria, Post Office Box 3055 STN CSC, Victoria, British Columbia V8W 3P6, Canada.
Characterization of a Novel Coronavirus Associated with Severe Acute Respiratory Syndrome


1National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA. 2Departments of Biochemistry and Biophysics, University of California–San Francisco, San Francisco, CA 94143, USA. 3Department of Virology, Erasmus University, Rotterdam, 3000 DR, The Netherlands. 4Department of Virology, Bernhard-Nocht Institute for Tropical Medicine, 20359 Hamburg, Germany.
Impact of 2003 Out-Break of SARS

• 8422 SARS cases with 916 deaths reported from 32 countries around the world

• 8 confirmed SARS cases in US with no death

• 23 genome sequences of different variations of SARS coronavirus have been sequenced and released at the NCBI web site

• All of these have been virtually identical with few changes in the nucleotides along the genome

• Genome of the SARS-CoV ‘Tor2 strain’ from Toronto and the ‘Urbani strain’ from Vietnam differ by just eight nucleotides

• Efforts to develop vaccines
Clinical Manifestation of SARS

• Short incubation period of 2-7 days

• Infection is usually characterized by flu-like symptoms, including fever, that may be accompanied by headache, muscle ache, dry non-productive cough and shortness of breath

• 20% of infected patients develop diarrhea

• Most SARS patients subsequently develop pneumonia

• Death occurs from progressive respiratory failure

• Overall fatality rate ranges from 10-15%
Mode of Transmission

- SARS is highly infectious
- Virus spreads primarily by close human contact
- Infection may also occur by SARS-CoV containing droplets which are released into the air via the coughing, or sneezing of the SARS patient
- Some specific medical procedures performed on SARS patient can also release virus-containing droplets into the air
- Touching a SARS-CoV infected surface and subsequently touching the eyes, nose or mouth may also lead to infection
Diagnostics

• SARS RNA can be detected in respiratory specimens

• Convalescent-phase specimens from SARS patients contain antibodies that react with the SARS-CoV

• NIAID-supported scientists in Hong Kong have developed a test that is able to detect the virus in respiratory aspirates and in fecal samples. Research is on going to improve the accuracy of this test.
Intensive and supportive medical care is the primary therapy.

No specific treatment has yet been shown to improve the outcome of the patients.

Screening for known and novel experimental anti-viral drugs and compounds.

Alpha interferon has been tested suitable for clinical evaluation.

Compounds targeting the SARS-CoV cysteine protease have also shown some promise.

Efforts are on-going to develop humanized antibodies against the SARS-CoV.

Baxter Healthcare and Aventis Pasteur are developing experimental inactivated whole virus SARS vaccine.

Protein Science Corporation is developing a recombinant subunit vaccine.
SARS-CoV

• Identified as a novel coronavirus, classified as a member of the *Coronaviridae* family in the order *Nidovirales*

• Enveloped, **positive**-sense, **single-stranded** RNA viruses with the **largest** RNA genome

• Genome range in length between **27** and **32 kb**

• **Replicate** in the **cytoplasm** of the animal host-cell

• Coronaviruses are the causative agent of **respiratory, neurological** and **enteric** diseases

• Virions measure between **100** and **140 nm** in diameter

• Most viral particles show characteristic appearance of **surface projections** which appears like a **crown**, from which these viruses have derived their name
Electron Micrograph of the SARS-CoV
Coronavirus Organization
Phylogenetic Reclassification of SARS-CoV

(Stadler et al., 2003)
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<td></td>
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<tr>
<td><strong>Group 1</strong></td>
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</tr>
<tr>
<td>Transmissible gastroenteritis</td>
<td>TGEV</td>
<td>Swine</td>
<td>Contact</td>
<td>Gastroenteritis</td>
<td>United States, Europe</td>
</tr>
<tr>
<td>Human coronaviruses 229, NL63</td>
<td>HCoV</td>
<td>Humans</td>
<td>Aerosols</td>
<td>Common cold</td>
<td>Americas, Europe</td>
</tr>
<tr>
<td><strong>Group 2A</strong></td>
<td></td>
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<tr>
<td>Human coronaviruses OC43, HKU-1</td>
<td>HCoV</td>
<td>Humans</td>
<td>Aerosols</td>
<td>Common cold</td>
<td>Americas, Europe</td>
</tr>
<tr>
<td>Murine hepatitis</td>
<td>MHV</td>
<td>Mice</td>
<td>Aerosols, contact</td>
<td>Gastroenteritis, hepatitis</td>
<td>Laboratory mouse colonies worldwide</td>
</tr>
<tr>
<td><strong>Group 2B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe acute respiratory syndrome</td>
<td>SARS</td>
<td>Bats, Humans</td>
<td>Aerosols, contact</td>
<td>Fever, pneumonia, severe respiratory disease</td>
<td>Asia, Americas</td>
</tr>
<tr>
<td><strong>Group 3</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Infectious bronchitis</td>
<td>IBV</td>
<td>Birds</td>
<td>Mechanical, oral–fetal</td>
<td>Bronchitis</td>
<td>Worldwide</td>
</tr>
<tr>
<td><strong>Torovirus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berne (equine torovirus)</td>
<td>EqTV</td>
<td>Horses</td>
<td>Oral–fecal</td>
<td>Diarrhea</td>
<td>Europe, Americas</td>
</tr>
<tr>
<td>Breda (bovine torovirus)</td>
<td>BoTV</td>
<td>Cattle</td>
<td>Oral–fecal</td>
<td>Diarrhea</td>
<td>?</td>
</tr>
<tr>
<td>Human torovirus</td>
<td>HuTV</td>
<td>Humans</td>
<td>?</td>
<td>Diarrhea</td>
<td>?</td>
</tr>
</tbody>
</table>

*Bats have been identified as the vertebrate reservoir, but disease is primarily in humans.*
SARS-CoV: Genomic Organization

(Stadler et al., 2003)
SARS-CoV Replicase

pp1a 4382 aa

pp1ab 7073 aa

PL2-pro

3CLpro

POL

HEL
SARS-CoV: Life Cycle of Coronaviruses
Papers for Discussion

Assignment

Imagine yourself to be retinoblastoma protein (Rb). Introduce your self, providing all relevant information such as your composition, size, role, significance in normal cell as well as in cancer biology. Provide testimonies regarding your role / significance. (Make a power point presentation. Please carry out appropriate research to respond to this question. Do not restrict yourself to HCV or this publication)

The students are assigned the following figures which they will present and discuss/ explain:

Temitayo Awoyomi: Fig 1

Marisa Fernandes: Fig 2

Camille Gentle: Fig 3

Steve Milord: Fig 4

LisaMarie Moore: Fig 5, 6, 7 (Supplemental DATA)

Piotr Pierog: Fig 8, 9 (Supplemental DATA)