Summary
Dave Cavanagh
***Coronaviridae*: a review of coronaviruses and toroviruses**

This chapter sets the scene for the other contributions in this book. Most aspects of the replication of coronaviruses, and to a lesser extent toroviruses, have been dealt with: from attachment to host cells, through RNA replication and transcription, protein synthesis, modification and transport, to assembly and release of new virions. I have tended to expand on those aspects that I believe are more relevant to SARS coronavirus as a novel and zoonotic virus e.g.: cell receptors for, and receptor-binding domains on, the spike glycoprotein; sequence relationships amongst coronaviruses; variation exhibited by the spike glycoprotein; determinants of pathogenicity, all relevant to the topic of the host range of SARS-coronavirus that is of such great interest; genome organisation, with particular regard to the non-structural, accessory proteins that are not required for replication *per se* but which might play crucial roles *in vivo*. Also included is a brief look at the diseases associated with coronaviruses, their rather broad tissue tropisms *in vivo*, experiments that show that the host range of coronaviruses in general is probably wide, and vaccine development.

Key words: SARS, coronavirus, spike protein, tissue tropism, accessory proteins, non-structural proteins, genome, transcription, coronaviridae, torovirus, infectious bronchitis virus, turkey coronavirus, transmissible gastroenteritis virus, feline coronavirus, canine coronavirus, human coronavirus, murine hepatitis virus, bovine coronavirus

Summary
Olaf Weber and Axel Schmidt
Coronavirus infections in veterinary medicine

The evidence that the SARS-coronavirus could be an animal coronavirus or could originate from an animal coronavirus has increased the level of interest for coronavirus infections in animals. Coronavirus infections have been recognized as causative agents for deadly diseases in farm animals -with important economic impact- and in pets for a long time.
This chapter reviews coronavirus infections in farm animals like swine (e.g. Transmissible Gastroenteritis), cattle, chicken (Avian Infectious Bronchitis) and turkeys (Bluecomb Disease) and describes some coronavirus infections in pets like dogs and cats (e.g. Feline Infectious Peritonitis). The last part of this chapter describes the Mouse Hepatitis Virus, one of the most important pathogens of small laboratory animals.

Summary
Princess Margaret Hospital SARS Study Group: Po Oi Lee, Ping Tim Tsui, Tak Yin Tsang, Tai Nin Chau, Chi Pong Kwan, Wai Cho Yu and Sik To Lai
Severe acute respiratory syndrome: clinical features

The main presenting features of Severe Acute Respiratory Syndrome (SARS) include abrupt onset of fever, flu-like symptoms and abnormal chest radiograph despite minimal respiratory symptoms. Chest radiography serves as a screening tool and monitor of disease progression in SARS. Lungs involvement can be focal, unilateral or bilateral multifocal. High resolution computed tomography (HRCT) of thorax is helpful when initial chest radiograph is negative despite high clinical suspicion. Diarrhea is rather common and may be attributed to the disease

process or side effects of medical treatment. Lymphopenia with normal or low total white cell count, thrombocytopenia, elevated liver enzymes are common laboratory findings. Twenty to 34 % of patients were treated in intensive care while 13-26 % required assisted ventilation. SARS runs a milder course in children an can be misdiagnosed in geriatric patients with atypical presentation. Advanced age, presence of comorbid conditions, high neutrophil count at presentation, high initial or peak lactate dehydrogenase level are associated with adverse clinical outcome.

Key words: clinical features, chest radiography, high resolution computed tomography (HRCT), adult respiratory distress syndrome (ARDS), steroids, ribavirin, prognostic factors, case fatality rate

Summary
Sherif R. Zaki and Cynthia S. Goldsmith
SARS coronavirus infection: pathology and pathogenesis of an emerging virus disease

This chapter presents the morphologic characteristics of SARS-CoV grown in tissue culture and the histopathologic changes, electron microscopic findings, and cellular localization of the virus in tissues from human patients and experimentally infected animals. In addition, the pathophysiology of SARS is discussed.

Key words: athology, electron microscopy, SARS coronavirus, immunohistochemistry, in situ hybridization, immunogold electron microscopy, animal model, pathogenesis

Summary
Caroline R. Astell, Steven J.M. Jones, Robert A. Holt and Marco A. Marra
Genome organization and structural aspects of the SARS-related virus

With the worldwide scientific community uncertain of what the causative agent was for SARS the Genome Sciences Centre at the BC Cancer Agency decided on March 27, 2003 to apply its high-throughput DNA sequencing capabilities to fully characterize the genome of this "new" virus.
A combination of oligo dT and random primers was used to create two libraries of cDNA clone. Clones were sequenced from both ends with appropriate primers and products resolved by electrophoresis on an automated sequencing instrument. The data, transferred electronically to the Bioinformatics team was processed and trimmed for sequence quality using PHRED software. Assembly of the sequence reads was carried out using the PHRAP sequence assembly software. The final sequence was analyzed using BLAST and FASTA to annotate the genome. The coding potential of the genome including the known and predicted viral proteins (total of 14 open reading frames in total) is discussed.
The unprecedented speed with which the sequence was generated (less than one week) demonstrates that this approach is an important one for the complete characterization of newly emerging pathogens as well as microbial bioterrorism agents.

Summary
Wolfgang Preiser, Christian Drosten and Hans Wilhelm Doerr
Virological laboratory diagnosis of SARS

Within weeks after the outbreak had started to spread across the globe, a novel coronavirus was isolated from SARS patients and soon recognised as the causative agent. At the same time, diagnostic tests for the detection of SARS-CoV in clinical specimens were developed. PCR sequences as well as reagents were made freely available to help stem the epidemic.
Although antibody detection is possible through different techniques such as neutralisation test, immunofluorescence assay and various enzyme immunoassays etc., it is not useful for diagnosis of acute suspected SARS cases. Virus isolation is relatively easy on commonly used cell lines (Vero, FRhK-4 etc.); however, it requires a biosafety level 3 laboratory.
Despite numerous research efforts to improve virus detection by means of viral nucleic acid testing, this remains problematic. Apart from the risk of false-positive results due to low test specificity or contamination, false-negative results pose a potential threat. Only low concentrations of viral RNA are detectable in readily available upper respiratory tract specimens (such as throat swabs) and in plasma during acute illness. Therefore, lower respiratory tract or faecal samples are preferable to increase sensitivity. The stringent guidelines published by WHO must always be followed.

Key words: diagnostic tests, laboratory diagnosis, antibody test, neutralisation test (NT), immunofluorescence assay, enzyme immunoassay, virus isolation, cell culture
Vero cells, biosafety safety level (BSL), nucleic acid testing, polymerase chain reaction (PCR) primers, respiratory tract specimens, SARS-CoV

Summary
Charlene E. Bush-Donovan, Tony Mazzulli, Jill J. Detmer and Johan Surtihadi
Performance evaluation of a Bayer Healthcare Diagnostics research-based SARS-coronavirus assay

Bayer Healthcare Diagnostics has developed a research based RT-PCR assay (Bayer) for detection and quantification of SARS-CoV. This article describes this assay, together with the assay's validation and performance and compares it with the RealArt™ HPA-Coronavirus LC RT-PCR Kit (Artus) for detection of SARS-CoV RNA in clinical specimens.
The results of this study show that the newly developed Bayer RT-PCR assay is very sensitive, detecting as few as 10 copies of SARS-CoV RNA and has a wide dynamic range (10 to 10^6 copies). Both the analytical and clinical specificities are 100%. There is no cross reactivity with other more common respiratory viruses and testing of clinical samples from non-SARS patients is negative.
Both the Artus and the Bayer assays are based on real-time PCR platforms and thus provide relatively rapid results. By standardizing the specimen processing and RNA extraction methods before performing either assay, we were able to show that both assays were highly correlated. The qualitative results (positive or negative) of the two assays were identical. The quantitative results of the Bayer Assay on the average were 0.14 logs (about 1.4 folds) higher than the Artus Assay. Additionally, although both assays have the same input volume of 5 µL of target into the amplification reaction, the copy number of the Bayer standards ranges between 10 to 10^6 copies/5 µL while the Artus Assay standards range between 50 to 5 x 10^4 copies/ 5 µL. The excellent correlation between these two assays, and the fact that the assays target different

genomic regions, suggests that each could be used to confirm a positive result obtained with the other, thus fulfilling the CDC requirement for a laboratory confirmed case of SARS.
Although at this writing there are no known human cases of SARS anywhere in the world, the potential for new cases to re-appear remains. The availability of properly validated, sensitive and specific assays is essential if new cases are to be accurately diagnosed particularly in light of the fact that the clinical definition of suspect and probable SARS remain very broad and somewhat non-specific.

Key words: quantitative RT-PCR, sensitivity, specificity, linearity, precision, performance comparison, clinical validation

Summary

Arhtur Chun-Wing Lau, Loletta Kit-Ying So and Loretta Yin-Chun Yam

Current status of therapy of SARS

The severe acute respiratory syndrome (SARS) caused by the SARS-associated coronavirus (SARS-CoV) has caused a worldwide outbreak in 2003. SARS has been postulated to cause a three-phased illness: viral replication phase, immunopathological phase and pulmonary destruction phase. Clinically, SARS presents with a wide spectrum of severity. There is no consensus on the types of pharmacological therapy which may be effective for SARS. A minority of patients with mild respiratory illnesses recover, either without any specific form of treatment or on antibiotic therapy alone. For the majority of patients with definite epidemiological links or microbiological confirmation, it may be prudent to administer an anti-viral agent (kaletra with or without ribavirin, and with or without interferon) as soon as SARS is diagnosed. An effective anti-viral agent may decrease the severity of the subsequent immunopathological damage and thus the need for salvage therapy with immunosuppressants. When patient has entered the immunopathological phase, an immunomodulatory agent (e.g. corticosteroids) will likely be indicated. The optimal choice, dosages and duration of such therapy are not known, but retrospective experience suggest that dosages may be titrated according to disease severity, and that sufficiently large dosages given for longer durations may be required for the more severe cases. Pulsed methylprednisolone may be effective as rescue therapy in case of unsatisfactory response or recurrence of respiratory failure after initial response. If response remains poor despite the above treatment, immunoglobulin or other forms of treatment may be tried. Assisted ventilation in the form of non-invasive ventilation should be instituted early if the clinical course is complicated with significant respiratory failure, provided the required environmental and personal protection measures are ensured. If response remains poor after 24 hours, elective intubation followed by mechanical ventilation should be considered. When fever recurs later in the course of SARS treatment, the clinical picture may not be easily distinguishable from superimposed bacterial or even fungal sepsis. Empirical anti-pseudomonal antibiotics would usually be indicated considering that the patient would have been put on immunomodulatory agents for some time. If clinical response is still not apparent and opportunistic infection is reasonably excluded, higher dosage of methylprednisolone can be considered in pulses for SARS rescue (e.g. methylprednisolone 1g for 2 days), especially if this had not been given previously. Subsequent to unprecedented collaborative efforts among medical and research communities worldwide, we have already gained a large amount of knowledge about this novel virus within the short space of just over a year. Randomized controlled treatment trials remain to be performed to improve our understanding of the most optimal treatment for this new disease.

Summary
Kanchan Anand, Haitao Yang, Zihe Rao and Rolf Hilgenfeld
Coronavirus main proteinase: target for antiviral drug therapy
(No summary & key words available)

Summary
Manfred H. Wolff, Syed A. Sattar, Olusola Adegbunrin and Jason Tetro
Environmental survival and microbicide inactivation of coronaviruses

Even though coronaviruses were first identified as respiratory pathogens of human in 1965, the recent discovery of the SARS coronavirus (SARS-CoV) has witnessed a sudden upsurge of interest in this virus group, and an urgent need to better understand the modes and vehicles for their spread for proper environmental control. Information from more recent but limited investigations with SARS-CoV and data from prior studies with other animal and human coronaviruses can be summarized as follows:
Current evidence strongly suggests that SARS-CoV spreads predominantly via droplets and such spread is easier to control than that by aerosols. Nearly 45% of human coronavirus 229E remained viable for one hour on the experimentally contaminated hands of adults; this is in contract to other enveloped respiratory viruses which became virtually undetectable in 10 minutes in similar experiments. SARS-CoV and other coronaviruses can also survive on porous and non-porous environmental surfaces for several hours under ambient conditions, but there is no evidence for their spread by either hands or environmental surfaces. Limited data available indicates that coronaviruses are more resistant to a variety of environmental surface disinfectants as compared to other enveloped viruses. Alcohol-based handrubs were able to reduce the viability titer of 229E by >4 $\log_{10}$ in 30 seconds on the hands of adults.
While there has been an accelerated accumulation of knowledge on human coronaviruses in general since the first reported outbreak of SARS, the precise means of their spread in mature still remain unknown. Such knowledge would be very useful in preventing and controlling the spread of SARS and other coronaviruses in the absence of safe and effective vaccination and chemotherapy.

Key words: aerosols, airborne spread, antisepsis, disinfection, droplet transmission, environmental control, environmental survival, human coronavirus 229E, microbicides, SARS coronavirus (SARS-CoV), virucidal activity

Summary
Andrea Ammon
Disease management strategies in SARS

Disease management in SARS aims at the early detection of new cases and the limitation of further spread of the disease. For an effective management strategy, the length of the incubation period (estimated median incubation period 4-5 days, maximum of 10 days), the period of infectiousness, the stability of the pathogen in the environment (at room temperature for at least 1-2 days), mode(s) and risk factors for transmission have to be taken into account. For SARS, a primary source in wildlife is suspected, the reservoir has not yet been found. The major mode of transmission seems to be direct contact with droplets, but certain procedures during health care may amplify transmission also via aerosols. To early detect cases, a surveillance system based on

an agreed case definition is necessary. In order to limit further the transmission from infected persons health care settings have to adhere strictly to infection control measures on a routine basis. Personal protective equipment of staff caring for SARS patients should consist of N 95 masks (eventually even higher protection), gloves, goggles and gown. Patients suspected with SARS should be isolated (obviously those with probable SARS). The indication for a SARS-CoV test should take into account that in low risk areas false positive test results are more likely. Access to the isolation unit should be restricted (essential staff only, limited number of visitors). Contact persons should be quarantined until SARS is ruled out in the index patient or the maximum incubation period since the last contact has elapsed. The SARS epidemic has sensitised health authorities world wide to strengthen the public health infrastructure. Training for health professionals should be continuously offered. Public health concepts like contact tracing, quarantine for exposed persons and isolation of cases should be evaluated. The containment of infectious diseases like SARS requires global cooperation.

Key words: incubation period, period of infectiousness, stability in the environment, mode of transmission, risk factors, infection control measures, personal protective equipment, isolation, SARS-CoV test, contact tracing, quarantine

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