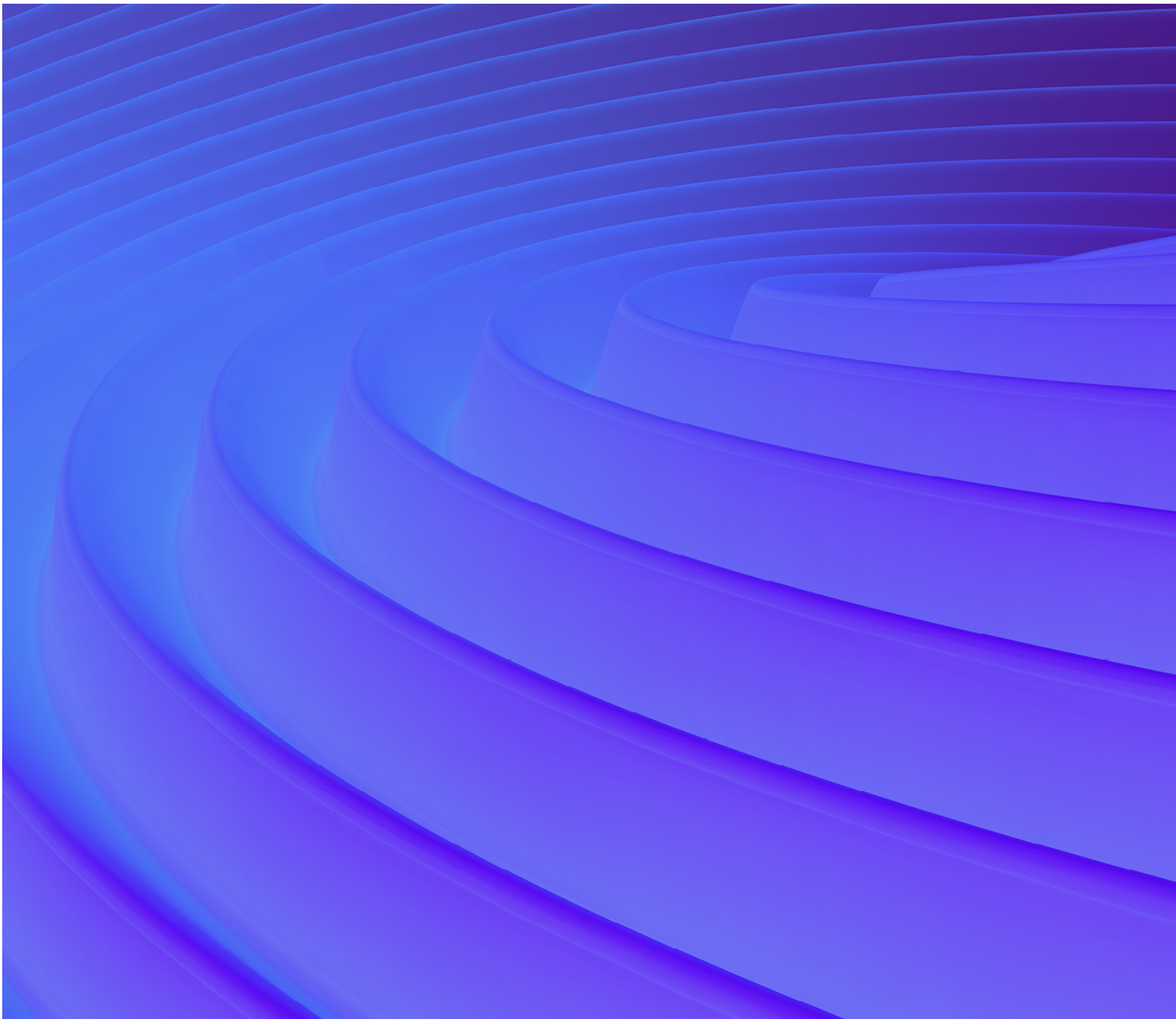


1/30/2020

Disease Briefing: Coronaviruses



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Coronavirus: Disease Briefings

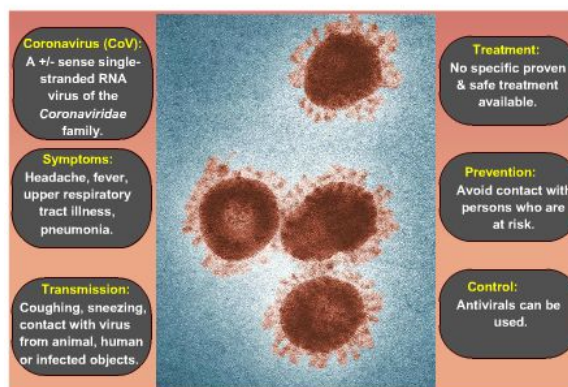
Facts about Coronaviruses

Coronaviruses are a group of large, enveloped, positive-sense, single-stranded RNA viruses belonging to the order Nidovirales, family Coronaviridae, subfamily Coronavirinae. Twenty-six different species are known (Cleri, D.J. et al (2010)) and have been divided into four genera (alpha, beta, gamma and delta) characterized by different antigenic cross-reactivity and genetic makeup. Only the alpha- and betacoronavirus genera include strains pathogenic to humans (Paules, C.I. et al (2020)).

The first known coronavirus, the avian infectious bronchitis virus, was isolated in 1937 and was the cause of devastating infections in chicken. The first human coronavirus was isolated from the nasal cavity and propagated on human ciliated embryonic trachea cells in vitro by Tyrrell and Bynoe in 1965. However, coronaviruses have been present in humans for at least 500-800 years, and all originated in bats (Chan, P.K. et al (2013); Berry, M. et al (2015))

Coronaviruses have long been recognized as important veterinary pathogens, causing respiratory and enteric diseases in mammals as well as in birds. Of the known coronavirus species, only six have been known to cause disease in humans: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory virus coronavirus (MERS-CoV) (Arabi, Y.M. et al (2017); Skariyachan, S. et al (2019)). The first four are endemic locally; they have been associated mainly with mild, self-limiting disease, whereas the latter two can cause severe illness (Zumla, A. et al (2016); Paules, C.I. et al (2020)). SARS-CoV and MERS-CoV are betacoronaviruses (Zumla, A. et al (2015)), and are among the pathogens included in the World Health Organization's list of high-priority threats (A research and development blueprint for action to prevent epidemics (World Health Organization, revised February 2018)).

Given the high prevalence and wide distribution of coronaviruses, their large genetic diversity as well as the frequent recombination of their genomes, and increasing activity at the human-animal interface, these viruses represent an ongoing threat to human health (Hui, D.S. et al (2020);). This fact again became evident in late 2019 and early 2020, when a novel coronavirus was discovered to be the cause of a large and rapidly spreading outbreak of respiratory disease, including pneumonia, in Wuhan, China ([WHO statement regarding cluster of pneumonia cases in Wuhan, China \(World Health Organization, January 9, 2020\)](#); [Emergencies: Novel coronavirus 2019 \(World Health Organization\)](#)). The virus, provisionally designated 2019-nCoV, was isolated and the viral genome sequenced. 2019-nCoV was characterized as a betacoronavirus, and thus became the seventh discrete coronavirus species capable of causing human disease ().



This 1975, digitally colorized transmission electron microscopical (TEM) image, depicted four avian infectious bronchitis virus (IBV) virions, which are *Coronaviridae* family members. IBV is a highly contagious pathogen, which infects poultry of all ages, affecting a number of organ systems, including the respiratory and urogenital organs. IBV possesses a helical genome, composed of non-segmented, positive-sense single-stranded RNA ((+) ssRNA).

Important RNA viruses and the diseases they produce in humans

Family/Characteristics	Viruses	Diseases
Orthomyxoviruses (Orthomyxoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; segmented genome)	Influenza A and B virus	Upper respiratory infection, croup
Paramyxoviruses (Paramyxoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)	Parainfluenza 1-3 virus Respiratory syncytial virus Measles virus Mumps	Upper respiratory infection, croup Upper respiratory infection, croup Measles Aseptic meningitis
Coronaviruses (Coronaviridae) Single-stranded RNA, enveloped (No DNA step in replication; positive-sense genome)	Human coronaviruses	Upper respiratory infection
Rhabdoviruses (Rhabdoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)	Rabies virus	Rabies
Picornaviruses (Picornaviridae) Single-stranded RNA, nonenveloped	Rhinoviruses Hepatitis A virus Enteroviruses: - Polioviruses - Coxsackie A24 viruses - Coxsackie B viruses - Coxsackie B1-5 viruses - Coxsackie A9 viruses - Echoviruses	Common cold Hepatitis Paralysis Acute hemorrhagic conjunctivitis Myocarditis, pericarditis Aseptic meningitis Aseptic meningitis Aseptic meningitis, encephalitis
Caliciviruses (Calciviridae) Single-stranded RNA, nonenveloped	Norwalk virus	Gastroenteritis
Hepeviruses (Hepeviridae) Single-stranded RNA, nonenveloped	Hepatitis E	Hepatitis
Togaviruses (Togaviridae) Single-stranded RNA, enveloped (No DNA step in	Alphaviruses (Group A arboviruses) Rubivirus	Encephalitis, hemorrhagic fever, chikungunya Rubella

replication; positive-sense genome)

Flaviviruses (Flaviviridae) Single-stranded RNA, enveloped (No DNA step in replication; positive-sense genome)	Group B arboviruses Hepatitis C virus Dengue virus Zika virus	Encephalitis, hemorrhagic fever Hepatitis Dengue fever Zika
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Bunyaviruses (Bunyaviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; segmented genome)	Some arboviruses Hantavirus	Encephalitis, hemorrhagic fevers Fever, renal involvement
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Reoviruses (Reoviridae) Double-stranded RNA, nonenveloped	Human rotaviruses	Gastroenteritis
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Arenaviruses (Arenaviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; segmented genome)	Lymphocytic choriomeningitis (LCM virus) Lassa virus	Meningitis Hemorrhagic fever
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Retroviruses (Retroviridae) Single-stranded RNA, enveloped (DNA step in replication)	HTLV-I, HTLV-II HIV-1, HIV-2	T cell leukemia, lymphoma, paresis AIDS
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Filoviruses (Filoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)	Marburg virus Ebola virus	Marburg disease Ebola hemorrhagic fever
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Morphology, Structure and Replication

Coronaviruses are so named because of their characteristic solar corona (crown-like) appearance when observed under an electron microscope. This appearance is produced by the peplomers of the spike [S] glycoprotein radiating from the virus lipid envelope (Chan, J.F. et al (2015)).

There are two major envelope proteins. The S glycoprotein is a major antigen responsible for both receptor binding and cell fusion (Song, Z. et al (2019)) and the transmembrane glycoprotein [M] is involved in budding and envelope formation; the M protein has also been found to play a pivotal role in virion assembly (Tseng, Y.T. et al (2010)). A few coronavirus species have a third glycoprotein, the haemagglutinin-esterase [HE]. The viral genome is associated with the basic phosphoprotein [N] within the capsid. The genome is non segmented, positive single-stranded RNA of about 26-32 kb, making it the longest RNA viral genome known, and contains from 7 to 10 different open reading frames. The RNA molecule has a methylated cap in 5' and a poly-A tail in 3' (Kilianski, A. et al (2014); Song, Z. et al (2019)).

Coronaviruses are capable of adapting quickly to new hosts through the processes of genetic recombination and mutation in vivo. As RNA viruses, coronaviruses rely on RNA-dependent RNA

polymerase (RdRp) to replicate the virus genome. The intrinsic error rate of RdRp is approximately 1,000,000 mutation/site/replication, resulting in continuous point mutations. Point mutations alone are not sufficient to create a new virus, however; this can only occur when the same host is simultaneously infected with two coronavirus strains, enabling recombination. One coronavirus can gain a genomic fragment of hundreds or thousands base-pair long from another CoV strain when the two co-infect the same host, enabling the virus to increase its ecological niche or to make the leap to a new species (Chan, P.K. et al (2013); Raj, V.S. et al (2014); Gralinski, L.E. et al (2015)). This susceptibility enabled the emergence in approximately two decades of three new human coronavirus species with epidemic potential: SARS-CoV, MERS-CoV and 2019-nCoV.

Epidemiology, Morbidity and Mortality

Coronaviruses, along with influenza, parainfluenza, RSV and rhinoviruses, cause mild, self-limited upper respiratory tract infections including the common cold (Chan, J.F. et al (2015)) and Pneumonia. Coronaviruses are responsible for 15-30% of all cold cases. Coronaviruses can also cause gastroenteritis in humans as well as a plethora of diseases in other animals (To, K.K. et al (2013); Berry, M. et al (2015)).

In a comprehensive epidemiology study conducted over a nine-year period in Sao Paulo, Brazil, human coronaviruses were detected in 7.7% of respiratory samples analyzed. The researchers looked at 1,137 samples obtained from asymptomatic individuals, general community, patients with comorbidities and hospitalized patients. NL63 was the most frequently detected coronavirus overall (50.0%), followed by OC43 (27.3%), albeit with variations by year: in 2004, HCoV-229E was the predominant strain circulating (61.5%) (Cabeça, T.K. et al (2013)).

A study of 559 upper respiratory samples obtained from adults with acute respiratory infections in Beijing, China in 2014 showed that HCoV-OC43 was present in 12.5%, with prevalence peaking in autumn (Hu, Q. et al (2014)).

An analysis of 686 adult patients presenting with acute respiratory infections in Mallorca, Spain (January 2013-February 2014) showed that 7% overall were caused by coronavirus, including 21.6% of patients in whom viral infection was implicated. The most prevalent strain identified was OC43 (50.0%), followed by NL63 (29%) and 229E (21%). Fifty-two percent of patients with CoV infections required hospitalization, and two patients required intensive care. No CoV infections were fatal in this study (Reina, J. et al (2014)).

A newly identified coronavirus that killed nearly 25,000 piglets in 2016-2017 in China emerged from horseshoe bats near the origin of the SARS-CoV, which emerged in 2002 in the same species of bats (*Rhinolophus* spp). The new virus, named swine acute diarrhea syndrome coronavirus (SADS-CoV), has not been confirmed to infect humans (Zhou, P. et al (2018)).

In late 2019, another new coronavirus began causing febrile respiratory illness in China. The virus, provisionally known as 2019-nCoV, was first detected in the urban center of Wuhan. Initial cases were traced to a seafood market, which was immediately closed. 2019-nCoV was sequenced and identified as a beta-coronavirus belonging to group 2B with at least 70% similarity in genetic sequence to SARS-CoV (Hui, D.S. et al (2020)). According to WHO, as of January 27, 2020, a total of 2,798 confirmed cases of 2019-nCoV had been detected worldwide, including 2,741 from China; another 5,794 suspected cases were reported in that country. Isolated and travel-related cases were reported in several countries including Thailand, Japan, the Republic of Korea, the U.S., Australia and Viet Nam. Also as of January 26, at least 80 deaths from 2019-nCoV had been confirmed in China. WHO deemed the risk assessment of this event to be very high in China, and high at both the regional and global level (Emergencies: Novel coronavirus 2019 (World Health Organization), consulted January 28, 2020; First travel-related case of 2019 novel coronavirus detected in United States (CDC press release, January 21, 2020)).

Facts about SARS-CoV

Severe acute respiratory syndrome (SARS) was a viral illness caused by a novel coronavirus and affecting the respiratory system. It originated in the Chinese province of Guangdong in November 2002, and was first reported at the beginning of 2003 in Asia, followed by reports of a similar disease in North America and Europe (Anderson, L.J. et al (2010); Heymann, D.L. et al (2013)). Worldwide, 33 countries and regions on five continents reported SARS cases, but the most affected country was China and in particular Hong Kong and Beijing. In spring 2003, SARS became a global health threat. The rapid spread of the virus to different continents after the initial outbreak underscored the ease with which infectious diseases can be spread internationally among members of our highly mobile global population (Hui, D.S. (2005); Cleri, D.J. et al (2010); Heymann, D.L. et al (2013)).

SARS Virus: Structure and Life Cycle

Animation available online

Although the disease has been absent since 2003, the rapid global spread of SARS demonstrated the need for ongoing surveillance of this and related coronavirus, as well as the maintenance of capacity for rapid response should it reemerge (Annual epidemiological report 2013: Reporting on 2011) surveillance data and 2012 epidemic intelligence data (European Centre for Disease Prevention and Control), consulted June 3, 2014). In the post-SARS era, the Chinese government has invested heavily in public health, infectious disease surveillance, response and reporting, enabling the country to respond more effectively to subsequent health threats such as H7N9 avian influenza (Zhang, Y. et al (2013)) and 2019-nCoV (Hui, D.S. et al (2020)).

The lessons learned from SARS have also been applied effectively on the international level in terms of response to the ongoing Middle East respiratory virus (MERS-CoV) outbreak, which emerged in 2012 and is caused by a different strain of coronavirus (Cheng, V.C. et al (2013); Al-Tawfiq, J.A. et al (2014); Zumla, A. et al (2015)). These lessons were again put to test in 2020 with the emergence and explosive spread of 2019-nCoV in China and globally.

Causative Agent: SARS Coronavirus

On March 24, 2003, scientists in Hong Kong and at the U.S. Centers for Disease Control and Prevention (CDC) reported the first preliminary evidence that a new coronavirus was the causative agent of SARS. On April 17, 2003, the WHO formally announced that the causative agent of SARS was a newly discovered member of the coronavirus family, which was not known to exist in humans before the disease was recognized. The new coronavirus was only distantly related to previously known and characterized coronaviruses (Falsey, A.R. et al (2003); Berry, M. et al (2015)).

The new coronavirus was named "Urbani SARS-associated coronavirus" in honor of Dr. Carlo Urbani, a WHO scientist who first reported the disease and subsequently died from SARS on March 29, 2003 (Reilley, B. et al (2003); Cleri, D.J. et al (2010)). Evidence based on many different methods, such as cell culture, microscopy, microarray data, serologic tests and PCR, supported the hypothesis that this new coronavirus was the causative agent of SARS (Gerberding, J.L. (2003)).

The absence of antibodies against the SARS virus in healthy people indicated that the virus had not previously circulated in the human population, providing additional supporting data for the possibility that SARS was caused by a new virus. The SARS virus was likely to have originated in animals, followed by either mutation or recombination events that facilitated infection of humans.

Investigators in both the U.S. and the Netherlands developed a model system of infection in monkeys in order to fulfill Koch's postulates. Experiments conducted at the Erasmus Medical Center of the University of Rotterdam gave the ultimate evidence that the SARS-CoV was the causative agent of SARS (Fouchier, R.A.M. et al (2003); Kuiken, T. et al (2003)).

SARS-CoV Morphology, Structure and Replication

The SARS-CoV virion is spherical with an average diameter of 78 nm. The helical nucleocapsid is enclosed by an envelope (Goldsmith, C.S. et al (2004)) that is covered with club-shaped, long peplomers about 20 nm long, giving it the typical crown-like appearance.

Coronaviruses enter cells via endocytosis and membrane fusion. ACE2 was identified as the cell receptor for SARS-CoV (Du, L. et al (2009); Kuba, K. et al (2010)). SARS-CoV entry into target cells is inhibited by polyanion compounds that have antiviral activity against other enveloped viruses. This data indicates that the SARS-CoV envelope proteins may have positive charges interacting with negative charges on the heparan sulfate proteoglycans present on the surface of target cells (Vicenzi, E. et al (2004)). The SARS-CoV requires acidification of endosomes for a productive infection, suggesting a pH-dependent mechanism (Simmons, G. et al (2004)). Coronaviruses replicate in the cytoplasm, where viral RNA is synthesized in a specific, flask-shaped compartment surrounded by a double membrane (Gosert, R. et al (2002)). The SARS-CoV infection is associated with ultrastructural changes both in vivo and in cultured cells. These changes include formation of double-membrane vesicles, presence of nucleocapsid inclusions and granulations in the cytoplasm (Goldsmith, C.S. et al (2004)).

The first gene to be translated is a viral RNA polymerase, called replicase, which initially transcribes full-length, negative strand (or antisense) copies of the genome. These negative strands are then used as templates to produce mRNAs that transcribe viral genes. Those subgenomic transcripts are nested, and have identical 5' regions, non-translated, and a poly-A tail in 3'. The different, nested transcripts are not produced by splicing, but by the activity of the viral RNA polymerase. The viral RNA polymerase interacts with a repeated intergenic sequence (TRS, transcription regulating sequence) located between the viral genes and allows the link between the 5' leader sequence and the start of each gene. The replication mechanism has not been completely described, but it is likely to proceed through subgenomic-size, minus-strand RNAs containing the anti-leader sequence. Large granular areas containing viral RNA and proteins that are not seen in cells infected by other coronaviruses may be observed in cells infected by the SARS-CoV. These regions may be viral translation centers (Goldsmith, C.S. et al (2004)).

The viral particles assemble in the Golgi, accumulate in dilated vesicles that are then transported and secreted to the cell surface, where they are released by exocytosis.

The SARS-CoV has biological characteristics that differ from previously known coronaviruses. SARS-CoV is tropic for Vero cells (a cell line derived from the African green monkey kidney epithelial cells), it grows at 37°C in contrast to other coronaviruses that grow at lower temperature, and can infect the lower respiratory tract (Vicenzi, E. et al (2004)). The SARS coronavirus genome is between 29705 and 29751 nucleotides ([NCBI Sequence Viewer: SARS coronavirus](#)). The SARS virus genome did not match any of the three previously known groups of coronaviruses, and had only a weak antigenic relationship to coronaviruses 229E and OC43. The polymerase gene is closely related to the bovine and murine coronaviruses in group 2, but also has some characteristics of avian coronaviruses in group 3. The SARS-CoV does not have a hemagglutinin-esterase present in group 2 and some group 3 coronaviruses, but it has a single papain-like proteinase that is present in group 3 coronaviruses (Holmes, K.V. et al (2003)). The differences between SARS-CoV and other coronaviruses pointed to a new group (Marra, M.A. et al (2003); Rota, P.A. et al (2003)) that was phylogenetically equidistant from the three known groups at that time. A new coronaviruses group 4 was proposed, of which the SARS-CoV is the only member. The discovery of SARS-CoV drove the search for other, previously unknown, human coronaviruses. Two such viruses were identified shortly thereafter: HCoV-NL63 (2004)

and HCoV-HKU1 (2005). Both appear to be distributed worldwide, and at least the former has been circulating in human populations for centuries (Perlman, S. et al (2009); Berry, M. et al (2015); Abdel-Moneim, A.S. (2014)).

The organization of SARS-CoV is similar to that of other coronaviruses, with the gene order being 5', replicase [rep], spike [S], envelope [E], membrane [M], nucleocapsid [N], 3', flanked by short untranslated regions (Du, L. et al (2009)). Sequences potentially coding for five more nonstructural proteins are interspersed between the ORF S and N.

The genome contains a total of 11 predicted open reading frames that potentially encode as many as 23 mature proteins (Ruan, Y.J. et al (2003)). The two principal ORFs, occupying about two-thirds of the genome, code for two major polyproteins, ORF1a and ORF1b. The polyproteins are cleaved by proteolysis to produce nonstructural proteins, the most important of which are the RNA-dependent RNA polymerase (Rep) and an ATPase helicase (Hel). The SARS-CoV has some genetic characteristics that are slightly different from other coronaviruses. There is a short anchor in the S protein, the number and location of the small ORFs are different, there is only one PLP-protease, and a unique, short lysine-rich region exists in the nucleocapsid protein. The biologic significance of these variations is unknown (Rota, P.A. et al (2003); Marra, M.A. et al (2003)).

The complete nucleotide sequence varied at only a few positions among different isolates of SARS-CoV (Rota, P.A. et al (2003)). Sequence analysis of isolates from Singapore, Canada, Hong Kong, Hanoi, Guangzhou and Beijing revealed two distinct strains that were related to the geographic origin of the virus (Ruan, Y.J. et al (2003)).

Origin of SARS-CoV

The fact that different animal coronaviruses are able to recombine their RNA to originate new viruses led to the hypothesis that SARS-CoV may have arisen as a result of a recombination event between an animal and a human virus (Hajjema, B.J. et al (2003); Chan, P.K. et al (2013)).

Early data suggested that SARS-CoV was related to bovine and murine hepatitis coronaviruses. However sequence studies of the entire genome did not reveal a bovine-murine origin. The SARS-CoV was determined to be a new, previously unknown pathogen that did not originate from already known strains (Ruan, Y.J. et al (2003)). It probably derived from an ancestor of the coronaviruses that naturally infected wild animals before crossing the species barrier to humans and causing SARS (Chan, P.K. et al (2013)).

How the virus became infectious for humans is unknown. The lack of sequence homology with any of the known human coronavirus strains makes a recombination event among human pathogens a remote possibility. By using methods such as Bayesian phylogenetic interference, it has been shown that the SARS-CoV genome has a recombination breakpoint within the RNA polymerase gene, and that the 5' region is related to mammalian and the 3' region to avian coronaviruses (Rest, J.S. et al (2003)).

In May 2003, scientists in Hong Kong reported the discovery of a virus virtually identical to the virus causing SARS in a rare species of civet (*Civettictis civetta*), a tree-dwelling cat. Yuen Kwok-Yung, a microbiologist at Hong Kong University, reported that the coronavirus had been found in the feces of masked palm civets, a nocturnal species found from Pakistan to Indonesia. The masked palm civet is considered to be a delicacy in southern China. Some of the first known cases of SARS occurred in November 2002 among food handlers who handled, killed and sold animals for food and chefs in Guangdong Province who were involved in the preparation of wild game for banquets. Infected civets are asymptomatic. The Hong Kong University team was able to culture a coronavirus almost identical to the SARS coronavirus from all 25 of the masked palm civets, representing eight different species that were tested (Enserink, M. (2003)).

Another team detected SARS-CoV-like viruses in live animals sold for food in the Guangdong province. The presence of the virus was confirmed in the Himalayan palm civet (*Paguma larvata*) and was found in a raccoon dog (*Nyctereutes procyonoides*) (Chan, P.K. et al (2013)). Sequence analysis showed a phylogenetic distinction between animal and human viruses, making passage from humans to the analyzed animals unlikely. This finding points to the possibility of

interspecies transmission route within animals held in the market, making the identification of the natural reservoir even more difficult. Subsequent studies suggested that the SARS-CoV had not been circulating in civets for long, and thus that some other species may be acting as a natural reservoir (Hui, D.S. et al (2010)); later investigations suggested that bats may be the reservoir species (Anderson, L.J. et al (2010); Wang, L.F. et al (2006)).

By serological analysis about 40% of wild animal traders and 20% of people employed in the slaughter of animals for market in the affected region had SARS-CoV antibodies, although none had SARS-like symptoms (Berry, M. et al (2015)). Therefore a SARS-like coronavirus had been present in the area at least two years before the SARS-outbreak. The virus, initially not infectious in the human population, may have evolved and adapted to humans to give rise to the SARS-CoV.

There appear to be at least three phases by which the virus adapted to the human host on a population basis. The first phase was characterized by cases of independent transmissions in which the viral genomes were found to be identical to those of the animal hosts. In the second phase, clusters of transmission among humans were observed that were characterized by a rapid adaptation of the virus to the human host. The third phase was characterized by the selection and stabilization of the genome, with one common genotype predominating throughout the epidemic (Unknown Author (2004)).

Transmission

The SARS coronavirus was transmitted through large droplets and via direct contact (Wong, S.S. et al (2008)). The virus can reach a concentration of about 100 million particles per ml in sputum (Drosten, C. et al (2003)) and can survive on contaminated surfaces and objects at room temperature for up to six days (Cleri, D.J. et al (2010)).

Two major factors contributed to the rapid spread of SARS. First, the international population is highly mobile as a result of air travel. Second, high urban population densities, especially on the Asian continent, make person-to-person contact frequent (Arita, I. et al (2003)).

SARS Virus: Structure and Life Cycle

Animation available online

Attack rates were higher than 50% in the healthcare setting during the outbreak, while household transmission was less efficient (6-8%) (Goh, D.L. et al (2004); Lau, J.T. et al (2004)). Simulation studies performed after the outbreak suggested that physicians and other health care workers were the principal vectors of SARS transmission in the hospital setting (Cleri, D.J. et al (2010)). Practices such as use of ventilators and nebulized bronchodilators may cause aerosols and spread of droplets containing virus. The risk of spreading the virus may also be increased by cardiopulmonary resuscitation, bronchoscopy, endotracheal intubation, airway and sputum suction (Loeb, M. et al (2004); Cleri, D.J. et al (2010); Chen, W.Q. et al (2009)). Nosocomial spread was reduced through use of surgical masks, gloves and gowns (Seto, W.H. et al (2003)).

Virus load and shedding peak at approximately 10 days from the appearance of clinical symptoms, when the patient's status worsens and requires medical attention. Thus patients are most infectious at the time of seeking health care (McDonald, L.C. et al (2004); Cleri, D.J. et al (2010)). Viral shedding continues for at least 13 more days (range 2-60 days) (Cleri, D.J. et al (2010)). Patients are not infectious during the incubation period (Zeng, G. et al (2009)).

A few patients were identified as SARS "superspreaders" who spread the virus efficiently because they harbored above-normal levels of virus. A superspreading event was believed to be involved in the rapid propagation of the virus in the Amoy Gardens apartment building outbreak, where more than 300 residents were infected, presumably by a single patient (Cleri, D.J. et al (2010)). Other superspreading events were reported in the Hotel Metropole in Hong Kong, among passengers on Air China flight 112 from Hong Kong to Beijing, and in an acute care hospital in Toronto, Canada (Braden, C.R. et al (2013)). Superspreading seems to be

associated with high virus titer, aerosol generation, contamination of the environment, and close contact with others in a healthcare setting (Cleri, D.J. et al (2010)).

Viral RNA may persist long after seroconversion, and could be detected in respiratory secretions, plasma and feces for some weeks (Drosten, C. et al (2003)). The SARS outbreak revealed the susceptibility of modern hospitals to nosocomial infections and emphasized the importance of implementing measures to reduce the risk of hospital infections (Gopalakrishna, G. et al (2004)).

Symptoms and Disease

The SARS-CoV preferentially infects the lower respiratory tract, resulting in a severe, acute viral pneumonia. The WHO case definition for probable SARS includes high fever ($>38^{\circ}\text{C}$) or history of fever in the previous 48 hours; new infiltrates on chest x-ray suggestive of pneumonia; flu-like symptoms (chills, cough, malaise, myalgia) or history of exposure to SARS-CoV; and one or more positive diagnostic tests for SARS (Cleri, D.J. et al (2010)). Unfortunately, the initial symptoms and clinical appearance are not easily distinguishable from other common respiratory infections, and fever may be absent in older adults.

Analysis of both autopsy samples and experimentally infected animals indicates that the SARS-CoV infection in the lung affects the pneumonic areas and is detected in type 2 pneumocytes (Gralinski, L.E. et al (2015)). In tissues SARS-CoV commonly causes diffuse alveolar damage, bronchial epithelial denudation, loss of cilia and squamous metaplasia. Giant-cell infiltration, hemophagocytosis and cytomegalic alveolar pneumocytes were also observed in some cases (Nicholls, J.M. et al (2003)). The infection progresses through an inflammatory or exudative phase (characterized by hyaline-membrane formation, pneumocyte proliferation and edema), a proliferative phase and a fibrotic phase (Gralinski, L.E. et al (2015)).

The respiratory tract was the main target of the SARS-CoV, although the gastrointestinal tract may also be involved (Zhang, D.M. et al (2008)). Infection of the central nervous system has been reported (Lau, K.K. et al (2004); Zhang, D.M. et al (2008)). Symptomatically, SARS generally followed a triphasic pattern that accompanies each of the phases in tissues. In the first week after infection, symptoms usually consisted of fever and myalgia. These early symptoms may have been related to direct viral cytopathic effects, since increases in viral load could be detected by PCR during this phase of the disease. Seroconversion was detected during the second week and was followed by a reduction of viral load. The innate immune response was insufficient to control the SARS-CoV infection because decreases in viral load are coincident with the specific antibody response (Peiris, J.S. et al (2003)). A third phase occurred in 20% of infected patients and was characterized clinically by disease progression that could not be explained by uncontrolled viral replication. This phase may be the result of the triggering of immunopathological damage by an exaggerated immune response that may be the ultimate cause of the SARS-associated lung damage (Gralinski, L.E. et al (2015)).

Symptoms of SARS during the 2003 outbreak were not identical in all patients. Nearly 100% of adults and children presented with fever, and approximately half with cough and/or myalgia. Only a few patients had upper respiratory symptoms. Diarrhea was reported in 11-15% of patients at presentation (Cleri, D.J. et al (2010)) and in up to 40-70% of hospitalized patients (Hui, D.S. (2005)). Lymphopenia, leukopenia, thrombocytopenia were detected in some patients. Elevation of enzymes such as lactate dehydrogenase, aspartate aminotransferase and creatinine kinase levels indicated an effect of SARS on the liver in some patients (Drosten, C. et al (2003); Cleri, D.J. et al (2010)). Others presented with symptoms unexpected in a respiratory infection, such as acute abdominal pain (Poutanen, S.M. et al (2003)). Pulmonary infiltrates were present on chest radiography. The changes in lung tissue pointed to damage inflicted by cytokines and chemokines (Gralinski, L.E. et al (2015)).

During the outbreak, about 40% of infected patients developed respiratory failure requiring assisted ventilation, however 90% of patients recovered within a week after the first appearance of symptoms. Smokers required mechanical ventilation more frequently than nonsmokers (Poutanen, S.M. et al (2003)). Older patients had greater morbidity and mortality, the result of an

aging-related attenuation in the adaptive immune response (Frieman, M. et al (2008); Schäfer, A. et al (2014)).

Fatal SARS was the result of progressive respiratory impairment caused by damage to the lung alveoli. While the mortality rate during the SARS outbreak was <1% for patients under age 24 (Hui, D.S. et al (2010)), it increased to about 13% in patients under age 60, and was much higher (approximately 50%) in those over 60 and in those developing acute respiratory distress syndrome (approximately 50%) (Cleri, D.J. et al (2010); Schäfer, A. et al (2014)). The overall mortality rate during the outbreak was approximately 10%. Fatal cases of SARS-CoV infection were characterized by aberrant interferon stimulation, persistent chemokine responses and dysregulated adaptive immune response (Schäfer, A. et al (2014)).

Independent correlates of adverse clinical outcome included known history of diabetes/hyperglycemia (Yang, J.K. et al (2006)), advanced age, male gender, comorbid hepatitis, high neutrophil counts at admission and high levels of lactate dehydrogenase, reflecting tissue necrosis related to the immune hyperactivity (Cleri, D.J. et al (2010); Hui, D.S. et al

(2010)). A positive association was reported between air pollution and higher case-fatality rates (Cleri, D.J. et al (2010)). Host genetic variants may have also influenced variations in disease response (Schäfer, A. et al (2014)).

SARS infection was less prevalent as well as less aggressive in young children (Berry, M. et al (2015)). The highest rates of infection occurred in people of 20-39 years of age, whereas only 1% of cases occurred in children under age 10 years (Liang, W. et al (2004)). High rates among young adults may reflect cases among healthcare workers, while similar high rates in older people may be the consequence of nosocomial infections.

A prospective, observational study reported in 2007 was the first to provide comprehensive information regarding the long-term outcomes of SARS survivors. The 117 SARS survivors from Toronto, Ontario, underwent physical examination, pulmonary function testing, chest radiography and the six-minute walk test, filled out quality-of-life surveys and provided information regarding healthcare utilization at three different points (3, 6 and 12 months) following hospital discharge. The results showed that most SARS survivors had recovered fully from the physical illness by one year. However, general health, vitality and social functioning were below normal in many SARS survivors one year after illness, and many patients reported being unable to return to their pre-SARS level of work. Health care utilization, especially with respect to psychiatric care, was significantly higher than normal during the period of evaluation, and patients reported important decrements in mental health. Family caregivers of SARS survivors also reported suffering psychological consequences (Tansey, C.M. et al (2007)). A later study of 22 long-term survivors in Toronto established that chronic post-SARS morbidity persisted for up to 20 months after onset of illness. Symptoms included chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep (Moldofsky, H. et al (2011)). A long-term follow-up study reported by Hong Kong researchers also found significant psychiatric morbidities and persistent fatigue in 233 SARS survivors at the fourth year of follow-up (Lam, M.H. et al (2009)); another Hong Kong follow-up study suggested that long-term impairment was more pronounced in health care workers (Ngai, J.C. et al (2010)).

Epidemiology and Cost of the SARS Epidemic

The WHO reported a total of 8,422 SARS cases and 916 resulting deaths in 33 countries worldwide during the period of the major outbreak between November 1, 2002 and August 7, 2003 (see [Summary table of SARS cases by country, 1 November 2002 - 7 August 2003 \(World Health Organization\)](#)). China was hardest hit, with at least 5,327 cases and 349 deaths (66% and 45% of the total, respectively) (Zhang, Y. et al (2013)). Epidemiologic studies estimated that the average incubation time was 6.4 days. Mortality was 6.8% in younger patients and was as high as 43% in patients over the age of 60 years (Cleri, D.J. et al (2010)). The global case-fatality rate was 11% (Wong, S.S. et al (2008)), albeit with significant variation between regions (Lau, E.H. et al (2010)).

The SARS epidemic had important economic implications. It has been estimated that the worldwide economic cost of the SARS epidemic was about USD 30 billion. The 6% annual economic growth of East Asia in 2003 was reduced to 5% during the epidemic (Kondro, W. (2003)). The total economic impact of SARS in China in 2003 has been estimated at USD 25.3 billion (Zhang, Y. et al (2013)), including losses to the tourism sector in Beijing alone estimated at USD 1.4 billion (Beutels, P. et al (2009)).

The rapid and effective containment of SARS just months after its international recognition was achieved thanks to an unprecedented international collaboration between researchers, healthcare providers and health authorities (Braden, C.R. et al (2013)). However, factors and circumstances that caused the emergence of SARS are not understood and a reemergence of the disease remains possible, particularly in light of the fact that animal reservoirs of the virus still exist (Lau, E.H. et al (2010); Berry, M. et al (2015)).

For more epidemiology information, consult the Incidence and Prevalence Database (IPD): [IPD: Severe acute respiratory syndrome \(SARS\)](#).

Facts about MERS-CoV

In September 2012, WHO reported two cases of acute respiratory illness, ultimately fatal, accompanied by renal failure and caused by a previously unknown human coronavirus (Milne-Price, S. et al (2014); Chan, J.F. et al (2015)). The earliest known case has now been traced to April 2012 (Chan, P.K. et al (2013)). The novel betacoronavirus responsible for the disease, formally named Middle East respiratory syndrome coronavirus (MERS-CoV), appears to have originated in bats (Zumla, A. et al (2015)) and uses dromedary camels as intermediate hosts (Cho, H. et al (2018)). Although it also pertains to the Coronavirinae family, the new virus was shown to be genetically different from the SARS coronavirus (Perlman, S. et al (2013)) and to use a different host-cell receptor, identified as dipeptidyl peptidase 4 (DPP4, also known as CD26) (Raj, V.S. et al (2013); Li, F. et al (2019)). In a human lung epithelial cell assay, MERS-CoV was shown to elicit a distinct pattern of host gene expression responses. The virus is a cause for concern due to its zoonotic potential and the high case fatality rate (approximately 35%) (Li, F. et al (2019)).

WHO has released interim guidelines for the appropriate care of patients suspected in whom this infection is suspected (see [Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus \(MERS-CoV\) infection is suspected - Interim guidance \(World Health Organization, 2019\)](#)). See [WHO Global Alert and Response \(GAR\): Coronavirus infections](#).

MERS-CoV Morphology, Structure and Replication

MERS-CoV is a positive-sense, enveloped, single-stranded RNA virus with a genome size of 29.9 kB. It is the first member of the betacoronavirus genus known to infect humans, and is more closely related to bat coronaviruses such as HKU4 and HKU5 than it is to SARS-CoV (Banik, G.R. et al (2015); Chan, J.F. et al (2015)). Seroepidemiology studies have failed to uncover evidence of past infections with MERS-CoV in the general population of the affected geographic region, supporting the affirmation that this is a new virus (Chan, J.F. et al (2015)).

The genome arrangement of MERS-CoV is 5' - replicase - structural proteins (spike - envelope - membrane - nucleocapsid) - poly(A) - 3', similar to other coronaviruses. The virus has 10 open reading frames (ORFs) and 16 putative nonstructural proteins that are involved in the processes of viral transcription and replication (Chan, J.F. et al (2015); Skariyachan, S. et al (2019)).

The virus gains entry into the host cell by binding to DPP4 receptors expressed in permission cell lines as well as in the kidney and other organs (Abdel-Moneim, A.S. (2014)). It uses host proteases to gain entry into lung cells. The protease furin activates the S protein on the viral envelope, mediating membrane fusion and enabling virus entry into the host cell (Banik, G.R. et al (2015)). Like the SARS-CoV, the Middle East respiratory virus is able to overcome the host

innate immune response until high virus titres have been achieved, and induces cytokine dysregulation (Gralinski, L.E. et al (2015); Skariyachan, S. et al (2019)).

Transmission

The MERS-CoV virus presumably originated in bats, although it was initially unclear how it made the leap from bats to humans (Abdel-Moneim, A.S. (2014)). CDC investigators were first to identify dromedary camels as an intermediate or amplifying host and the most likely source of zoonotic transmission in the Middle East (Adney, D.R. et al (2014); Banik, G.R. et al (2015); Arabi, Y.M. et al (2017)). Several possible routes of spread exist, including direct contact with the animals--particularly juvenile camels--and their bodily fluids, as well as meat handling and/or consumption of unpasteurized camels' milk (Zumla, A. et al (2015); Widagdo, W. et al (2019)).

Although it is primarily a zoonotic virus, nonsustained human-to-human transmission has been confirmed in 53-60% of all cases, albeit predominantly in health care settings and family clusters (Zumla, A. et al (2016); Arabi, Y.M. et al (2017)). Patients with severe to fatal infection are more likely to transmit the virus, since they shed a higher amount of virus progeny in comparison to those with asymptomatic or mild infection (Widagdo, W. et al (2019)). Like SARS-CoV, droplets are believed to constitute the principal mode of transmission of MERS-CoV (Cho, H. et al (2018)). Nosocomial spread, i.e. contamination via contact with virus on environmental surfaces, was also confirmed during the Korean outbreak in 2015 (Bin, S.Y. et al (2016); Cho, H. et al (2018)).

Symptoms and Disease

The incubation period is approximately 5 days (range 2-15 days), with 94% of patients showing signs of disease by day 12 (Chan, J.F. et al (2015)). Typical presenting symptoms are nonspecific and include fever, chills, nonproductive cough, dyspnea, rigor, headache, myalgia and malaise. Some patients present with gastrointestinal symptoms, including diarrhea, nausea and vomiting, and abdominal pain. Acute renal impairment is a unique feature of MERS and occurs with significantly greater frequency than was seen in patients with SARS (Al-Tawfiq, J.A. et al (2014); Chan, J.F. et al (2015)).

Symptoms and manifestations of Middle East respiratory syndrome range from mild or asymptomatic infection to severe pneumonia, acute respiratory distress, septic shock and multiorgan failure resulting in death (Zumla, A. et al (2015); Zumla, A. et al (2016)). Respiratory failure with ARDS and multiorgan dysfunction syndrome are not uncommon, and the majority of patients with these complications will require admission to the intensive care unit within 2-5 days of symptom onset. The median time from symptom onset to invasive ventilation and/or extracorporeal membrane oxygenation in these patients is 4.5 to 7 days (Chan, J.F. et al (2015)). Risk of severe disease is higher in men over age 45, people with preexisting medical conditions including diabetes, obesity chronic kidney disease, chronic cardiac disease and COPD (Chan, J.F. et al (2015); Zumla, A. et al (2016)), and in health care workers.

While the early case-fatality rate was close to 60%, this has decreased with improved awareness and surveillance; however, mortality remains above 35% (Al-Tawfiq, J.A. et al (2014); Chafekar, A. et al (2018)). The probability of a fatal outcome is much greater among patients aged 50 years and older as compared to younger patients (77% vs. 22%, respectively) (Cauchemez, S. et al (2014)). Mortality is also higher in men and in patients with multiple comorbidities (Banik, G.R. et al (2015); Chan, J.F. et al (2015)).

Epidemiology of MERS

Since September 2012, cases of MERS-CoV have been reported in 27 countries including Italy, the Netherlands, France, Germany, Italy, Tunisia, Malaysia, United Kingdom, United States, Iran, Egypt, Lebanon and Turkey (Chafekar, A. et al (2018);); [Middle East respiratory syndrome coronavirus \(MERS-CoV\) \(World Health Organization\)](#), consulted April 10, 2019). Initial cases were restricted to the Middle East as well as two cases in the U.K. among family members of an

infected individual who had recently traveled from Saudi Arabia. Several cases later occurred in clusters, including a hospital outbreak in Saudi Arabia, and confirmed that the virus can be transmitted between humans during close contact (Assiri, A. et al (2013); Zumla, A. et al (2015)). As of November 2019, the World Health Organization had been notified of 2,494 laboratory-confirmed human cases of infection with the virus and 780 related deaths (case-fatality rate 37.1%) (Middle East respiratory syndrome coronavirus (MERS-CoV) (World Health Organization), consulted January 28, 2020).

Published epidemiology figures reflect only the number of patients with clinical manifestations of MERS. However, a study of the general population of Saudi Arabia suggests that the rate of asymptomatic disease is much higher. Based on a serosurvey of individuals aged 15 and older who were seen by a health care professional or participated in a national burden-of-disease study between December 2012 and December 2013, nearly 45,000 people in that country were estimated to be seroprevalent for MERS-CoV, and may constitute a source of infection for individuals who do not come into contact with camels (Müller, M.A. et al (2015)). Moreover, a study of travelers to countries affected by MERS between September 2012-2016 has enabled a more precise estimate of the number of severe MERS cases in those countries (Saudi Arabia, United Arab Emirates, Jordan and Qatar). The researchers estimated that approximately 3,300 cases of severe disease occurred in that span of time, a number that is 2.3 times greater than the total number of laboratory-confirmed infections (O'Hagan, J.J. et al (2016)).

On May 20, 2015, the index case in what became the largest outbreak of MERS-CoV outside the the kingdom of Saudi Arabia was reported in the Republic of Korea. The index patient had recently traveled to four countries in the Middle East, and returned to Korea while still asymptomatic. As of September 11, WHO had been notified of the existence of 185 laboratory-confirmed cases, including 36 fatalities, in Korea, as well as an additional case in China (Middle East respiratory syndrome coronavirus (MERS-CoV) (World Health Organization)).

The epidemiology of new MERS infections appears to follow a seasonal pattern, with outbreaks in the spring of 2013, 2014 and 2015 coinciding with the months when camels give birth (Al-Tawfiq, J.A. et al (2014)).

Although the data is still evolving, the basic reproduction number (R_0) for the MERS-CoV is generally considered to be less than 0.7, indicating low pandemic potential unless the virus mutates. Nonetheless, experts advise increased surveillance and active contact tracing as well as thorough investigation into potential animal hosts and routes of zoonotic reinfection, which appears to be perpetuating the outbreak (Breban, R. et al (2013); Zumla, A. et al (2015); Chan, J.F. et al (2015)). With an R_0 of less than 1, chains of disease transmission are not self-sustaining in the presence of effective infection control measures (Zumla, A. et al (2015)). For more epidemiology information, consult the Incidence and Prevalence Database (IPD): [IPD: Middle East respiratory syndrome coronavirus \(MERS-CoV\)](#).

Facts about 2019-nCoV

In late 2019, a new coronavirus began causing febrile respiratory illness in China. The virus, provisionally known as 2019-nCoV, was first detected in the urban center of Wuhan. Initial cases were linked to a wholesale seafood market, which was immediately closed. 2019-nCoV was sequenced and identified as a betacoronavirus belonging to the sarbecovirus subgenus, with 75-80% similarity in genetic sequence to SARS-CoV (Hui, D.S. et al., 2020; Zhu, N. et al., 2020; Perlman, S., 2020). The as-yet-unidentified animal host of 2019-nCoV is presumed to be a bat; an intermediate host may also have been involved (Perlman, S., 2020). Although the initial cases were traced to zoonotic transmission, human-to-human transmission was soon documented, both in healthcare settings and in familial clusters.

Following an incubation ranging from 2-14 days, 2019-nCoV infection manifests as respiratory illness ranging from mild to severe, with symptoms that include fever, cough and dyspnea. Chest CT scan reveals the presence of bilateral ground-glass opacities (Huang, C. et al., 2020; [Centers for Disease Control and Prevention \(CDC\) – 2019 novel coronavirus, Wuhan, China](#)). In an early description of 41 clinical cases, patients had serious, sometimes fatal, pneumonia.

Clinical presentations were very similar to those of SARS-CoV. Patients with the most severe illnesses developed acute respiratory distress, requiring ICU admission and oxygen therapy. The mortality rate in this early patient set was approximately 15% (Huang, C. et al., 2020), and primarily involved patients with serious underlying illnesses or conditions (Munster, V.J. et al., 2020).

According to WHO, as of January 28, 2020, a total of 4,593 confirmed cases of 2019-nCoV had been detected worldwide, including 4,537 from China; another 6,973 suspected cases were reported in that country. The recognition of infections in healthcare workers first confirmed human-to-human transmission. Isolated and travel-related cases were reported in several countries including Thailand, Japan, the Republic of Korea, the U.S., Australia and Vietnam. Also as of January 28, at least 106 deaths from 2019-nCoV had been confirmed by WHO. The risk assessment of this event was deemed by WHO to be very high in China, and high at both the regional and global level (Emergencies: Novel coronavirus 2019 (World Health Organization), consulted January 29, 2020; First travel-related case of 2019 novel coronavirus detected in United States (CDC press release, January 21, 2020)). China CDC reported somewhat higher numbers (5,974 confirmed and 9,239 suspected cases; 132 fatalities) (Tracking the epidemic (China CDC), consulted January 29, 2020).

Although the early case-fatality rate appeared to be low, the rapid spread and ease of transmission of the virus, even by asymptomatic individuals, is causing global alarm: experts point out that although a virus may pose a low health threat at the individual level, if easily transmissible it can nonetheless pose a significant risk at the population level. Given its pandemic potential, careful surveillance of 2019-nCoV is critical to monitor its future host adaption, viral evolution, infectivity, transmissibility and pathogenicity (Huang, C. et al., 2020).

Interim guidelines for the appropriate care of patients in whom this infection is suspected are available from WHO (Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected - Interim guidance (World Health Organization, January 12, 2020)) and CDC (Interim infection prevention and control recommendations for patients with known or patients under investigation for 2019 novel coronavirus (2019-nCoV) in a healthcare setting (Centers for Disease Control and Prevention, January 2020)).

Diagnosis

Until standardized reagents for detection of both virus and antibody became available, SARS diagnosis was based on the basis of clinical symptoms together with a positive epidemiological history (Cleri, D.J. et al (2010)). Symptoms associated with SARS are high fever (>100.4°F/38°C), cough and difficulty breathing. Diagnosis may be confirmed by chest radiography if there is evidence of infiltration consistent with pneumonia or respiratory distress syndrome.

During the SARS epidemic, the FDA and CDC collaborated on the validation and licensing of SARS diagnostic tests. Approaches to diagnostic testing include serologic detection, virus isolation in cell culture, electron microscopy and detection of viral RNA by molecular methods. Both ELISA and immunofluorescent serologic tests for detecting coronavirus antibodies were developed (Suresh, M.R. et al (2008)). Some patients develop detectable anti-SARS virus antibodies within two weeks after symptoms, but a definitive negative diagnosis could not be obtained until three weeks after the onset of fever.

The diagnostic tests for detection of the SARS-CoV have all some limitations. ELISA detects SARS-CoV antibodies but only about 20 days after the onset of symptoms and is only useful for confirmation of SARS but not for rapid diagnosis. The immunofluorescence assay (IFA) can detect antibodies after 10 days from the onset of symptoms in serum of infected patients. However serologic testing is the only available laboratory test for excluding a diagnosis of SARS. If sera are negative for antibody four weeks after onset of symptoms, the disease is not SARS

(Jernigan, J.A. et al (2004)). Neither virus isolation in cell cultures nor electron microscopy are sensitive enough for general diagnostic use and both methods are inconvenient.

The availability of RNA sequence information on a number of strains of SARS viruses facilitated the development of rapid diagnostic tests. Molecular tests based on reverse transcription polymerase chain reaction (RT-PCR) specifically detect viral RNA. RT-PCR is the only early detection test available, but its sensitivity is low, identifying only 37.5-50% of probable SARS cases (Suresh, M.R. et al (2008)). Detection of viral RNA increases and peaks after about 10 days from the onset of the disease. The virus remains detectable in respiratory secretions for more than one month in some patients, but after three weeks cannot be recovered for culture. In the initial phase that occurs in the first week postinfection, the virus may be detected in nasopharyngeal aspirates, throat swabs and sputum samples, while in later phases viral RNA may be more easily detected in stool samples (Chan, K.H. et al (2004)).

RT-PCR is currently the only rapid diagnostic test that can give the necessary sensitivity and specificity that are required for a routine clinical diagnostic tool; two-step conventional and one-step quantitative RT-PCR techniques were routinely used during the outbreak (Peiris, J.S. et al (2008)). A report from the CDC indicated that real-time RT-PCR may be more sensitive than conventional RT-PCR, potentially providing a useful technique for detecting virus in the early phases of the diseases, when virus titer is low (Emery, S.L. et al (2004)). ELISA detection of anti-nucleocapsid protein (NP) antibodies, which peak early in infection, has been identified by Canadian investigators as a more reliable and specific method of diagnosing SARS (Suresh, M.R. et al (2008)).

Various diagnostic tests have been used in the detection of MERS-CoV infection, including serological assays, immunofluorescence assays, ELISA, protein microarray, micro-neutralization assays and Western blot—all of which have limitations (Banik, G.R. et al (2015))—, as well as RT-PCR, which is most specific and sensitive (Skariyachan, S. et al (2019)). In June 2013, the U.S. FDA granted emergency use authorization for the CDC Novel Coronavirus 2012 Real-time RT-PCR Assay, which can be used by qualified laboratories to detect MERS-CoV in respiratory, blood and stool specimens. WHO recommends that screening RT-PCR target the upE gene, and that positive samples be retested targeting the ORF1a, ORF1b or N gene. Testing should use samples obtained from the lower respiratory tract, e.g., bronchoalveolar lavage or tracheal aspirate, where viral load is greatest (Banik, G.R. et al (2015); Zumla, A. et al (2015)). However as the procedure for collecting these specimens is invasive, upper respiratory specimens are sometimes used instead (Chan, J.F. et al (2015)).

Researchers at the University of Texas and NIH have developed asymmetric five-primer reverse transcription loop-mediated isothermal amplification (RT-LAMP) assays for the detection of MERS-CoV. The RT-LAMP assays are designed to amplify MERS-CoV genomic loci located within the ORF1a and ORF1b genes and the upE gene, and will enable the development of portable point-of-care diagnostics (Bhadra, S. et al (2015)).

Differential Diagnosis

Pneumonia of other viral or bacterial origin—especially *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, methicillin-resistant *Staphylococcus aureus* and *Legionella* spp.—must be included in the differential diagnosis of SARS. Other febrile viral diseases that should also be included in the differential diagnosis include seasonal and avian Influenza, Respiratory Syncytial Virus, Varicella Zoster Virus, human metapneumovirus and hantavirus. When appropriate, other epidemic or population-wide diseases may also need to be taken into consideration, e.g. smallpox (see Poxvirus), tularemia, Anthrax, viral hemorrhagic fever or plague (Cleri, D.J. et al (2010)).

Prevention

Without effective drugs or vaccines against the infectious agent, physical interventions such as isolation and quarantine are the most effective means of controlling a coronaviral infections with epidemic potential (Jefferson, T. et al (2010); Chan, J.F. et al (2015)); however, patients are

typically asymptomatic during the incubation period, which ranges from 2-14 days (mean 4 days) in the case of SARS (Cleri, D.J. et al (2010)) and from 2-15 days (mean 5 days) in the case of MERS (Banik, G.R. et al (2015)). Authorities are often reluctant to impose these measures because of their economic and social impact; however, without other means of control of the epidemic spread of SARS, there was no alternative. The success of these measures was demonstrated in Singapore, where application of infection control measures resulted in a decrease in the reproduction number (secondary infection rate) from 7 at week 1 to <1 after week 2 (Cleri, D.J. et al (2010)). In Taiwan, the application of Level A quarantine (that of potentially exposed contacts of suspected SARS patients) resulted in the prevention of approximately 461 additional cases and 62 additional deaths; the use of Level B quarantine (that of travelers arriving from affected areas), in contrast, reduced the number of new cases and deaths by only about 5% (Hsieh, Y.H. et al (2007)). CDC recommends use of airborne infection isolation procedures in the care of all confirmed MERS infections in that country (Al-Tawfiq, J.A. et al (2014)).

Hygienic measures are recommended to prevent the spread of disease in situations where individuals are in contact with patients or contaminated fomites. Washing hands with soap and water or with alcohol-based handrubs is effective for interrupting virus transmission. The SARS virus is able to survive on surfaces for up to six days, but can be inactivated by washing with bleach, 75% ethanol, household detergents (Cleri, D.J. et al (2010)), chemical disinfectants such as povidone-iodine, or heating (Wong, S.S. et al (2008)). The MERS virus is capable of surviving for up to 48 hours at 20°C and for 24 hours at 30°C (Chan, J.F. et al (2015)). Personal protective equipment, including eye protection, is recommended for health care personnel, as well as surgical masks or N-95 disposable filtering respirators (Chan, J.F. et al (2015)). Airborne precautions should be applied especially when performing aerosol-generating procedures such as intubation (Ben Embarek, P.K. et al (2015)). All potentially infectious specimens should be handled and transported with caution, and must be tested in laboratories meeting WHO BSL3 standards (Chan, J.F. et al (2015)).

As a result of the SARS outbreak, WHO revised the rules for reporting infectious diseases by its member states. The previous reporting requirements, formulated in 1951, required reporting for plague, cholera and yellow fever only, and the resulting delay in reporting cases early in the outbreak was likely to have contributed to its rapid spread (Enserink, M. (2003)). The efficient and collaborative international response to the MERS outbreak a decade later testifies to the improvements made (Chan, J.F. et al (2015)).

Vaccines

The successful containment of coronavirus epidemics in farm animals by vaccines, by either killed or attenuated virus, points to the potential success of vaccine programs.

The S protein is currently considered to be one of the most promising targets for coronavirus vaccine development (Song, Z. et al (2019)), and is being targeted for the development of anti-MERS-CoV vaccines (Ma, C. et al (2014); Zhang, N. et al (2015)), including mucosal vaccine for intranasal administration (Ma, C. et al (2014)). This research has been facilitated by the recent development of small animal models that effectively replicate MERS-CoV transmission and symptomatic human disease (Schindewolf, C. et al (2019)). Human MERS-CoV vaccines are also now in development, including DNA vaccines, vector-based, live attenuated and protein subunit vaccines (Cho, H. et al (2018); Schindewolf, C. et al (2019)); many of these vaccines target the S protein (Li, F. et al (2019); Song, Z. et al (2019)).

Research by scientists at the University of Pittsburgh School of Medicine and the Graduate School of Public Health in collaboration with CDC showed that an adenoviral-based vaccine could induce both SARS-CoV-specific T cell and virus-neutralizing antibody responses (Gao, W. et al (2003)). Both responses have been found important for lasting protection. In long-term studies of recovered SARS patients, antibody responses waned after approximately six years, while T-cell responses persisted, suggesting that the latter is required for long-lasting immunity (Zumla, A. et al (2015)).

In the case of the MERS-CoV outbreak in the Middle East, the development of a vaccine for use in camels has also been prioritized, in order to interrupt the ongoing zoonotic transmission of the disease (Zumla, A. et al (2016); Wirblich, C. et al (2017)).

The following table presents an up-to-date overview of the development of potential coronavirus vaccines.

Experimental coronavirus vaccines in active preclinical and clinical development

Drug name	Organisations	Description	Phase
Convalescent plasma	King Abdullah International Med Res Cent	Plasma from patients who recently recovered from Middle East Respiratory Syndrome Corona virus (MERS - CoV)	Phase II
GLS-5300	Inovio Pharmaceuticals; GeneOne Life Science	Middle East Respiratory Syndrome DNA vaccine using the SynCon (TM) technology, encoding MERS spike protein	Phase I/II
ChAdOx1 MERS	Vaccitech Ltd.; University of Oxford	Middle East respiratory syndrome recombinant (MERS) vaccine consisting of replication - deficient simian adenovirus vector ChAdOx1 carrying full - length spike gene of MERS - CoV camel isolate; under the control of human cytomegalovirus major immediate early promoter (IE CMV)	Phase I
MVA-MERS-S	Ludwig-Maximilians-Univ. Muenchen	Middle East respiratory syndrome coronavirus (MERS - CoV) vaccine comprising modified vaccinia virus encoding full - length S protein of MERS - CoV, under the control of early/late promoter PmH5	Phase I

GREVAX/MERS	Greffex	Recombinant adenoviral vector developed using GREVAX Universal Platform (GREVAX vector) encoding Middle East respiratory syndrome coronavirus (MERS - CoV) antigens	Preclinical	
MVA-MERS-S_DF1	Universitaetsklinikum Hamburg-Eppendorf	Middle east respiratory syndrome (MERS) vaccine consisting of a modified vaccinia ankara (MVA) virus encoding MERS - CoV spike (S) protein antigens	Preclinical	13

Treatment

There is no approved drug therapy for SARS, MERS or any other coronavirus infection at this time, and there is a paucity of clinical trial data upon which to base treatment decisions. Supportive care is the mainstay of treatment for patients with severe disease (To, K.K. et al (2013); Arabi, Y.M. et al (2016); Momattin, H. et al (2019)).

When it emerged in 2003, SARS was an unknown disease and treatment was empirical (Hui, D.S. (2005)). Initial efforts to treat the disease with broad-spectrum antibodies from human immune serum globulins were unsuccessful. Some nonspecific immunosuppressive treatments or broad-spectrum antiviral agents, such as ribavirin, were of limited success (Lee, N. et al (2003); So, L.K. et al (2003)). Combination therapy with ribavirin and corticosteroids was frequently administered as first-line treatment for SARS, based on promising results observed in some of the earliest patients treated, although data obtained subsequently failed to confirm ribavirin's anticipated anti-SARS-CoV activity in vitro (Cleri, D.J. et al (2010); Tai, D.Y. (2007)). Some physicians preferred to delay administration of corticosteroids until the second week of infection in order to reduce side effects. The HIV protease inhibitor Kaletra (lopinavir/ritonavir) was also used in combination with ribavirin or as monotherapy in an attempt to block SARS-CoV viral replication. Nelfinavir, another HIV protease inhibitor, was proposed as an alternative (Hui, D.S. (2005)).

In response to a request by the World Health Organization, a systematic review was made of all published reports of treatments that were used during the 2002-2003 SARS epidemic, as a tool to guide future treatment decisions and identify research priorities. The drugs reviewed included ribavirin, corticosteroids, lopinavir/ritonavir, type I interferon (IFN), intravenous immunoglobulin (IVIG) and SARS convalescent-phase plasma. A total of 54 SARS treatment studies, 15 in vitro studies and three acute respiratory distress syndrome (ARDS) studies were identified for inclusion. Although some of the in vitro studies indicated potential antiviral efficacy for ribavirin, lopinavir and type I IFN in tissue culture, none of the clinical studies supported these findings. In the case of ribavirin, 26 trials were inconclusive and four suggested potential harm. In the case of steroids, 25 studies were inconclusive and four indicated possible harm. Studies on convalescent plasma, IVIG, type I IFN and lopinavir/ritonavir were also inconclusive. The researchers concluded that in spite of an intensive literature review, no conclusive evidence was

obtained to support the efficacy of any drug used in the treatment of patients with SARS. They emphasized that clinical trials should be designed to validate a standard treatment protocol for possible future outbreaks, in order to standardize doses and timing of treatment and to facilitate data accrual and the monitoring of specific adverse effects and potential benefits of specific therapies (Stockman, L.J. et al (2006)). Should the virus reemerge, patients with recognized SARS infection should be isolated in negative-pressure single rooms and appropriate, well-fitting face masks should be used to minimize potential for transmission of the virus through respiratory secretions (Cleri, D.J. et al (2010)).

Repurposing of known drugs with proven safety records is a faster and more efficient way of developing drugs in an outbreak situation, when time is of the essence. In light of the MERS-CoV outbreak, NIH researchers screened a panel of 290 approved and investigational drugs with defined cellular targets in order to determine the potential for repurposing any of them to treat SARS and/or MERS. They found that 33 compounds were active against MERS-CoV, 6 against SARS-CoV and 27 against both coronaviruses. The active drugs were grouped into 13 therapeutic classes and included antibacterial and antiparasitic agents, neurotransmitter inhibitors, estrogen receptor antagonists, kinase signalling inhibitors, inhibitors of lipid or sterol metabolism, protein-processing inhibitors, and inhibitors of DNA synthesis/repair (Dyall, J. et al (2014)). In another repurposing study, Dutch investigators screened a library of 348 FDA-approved drugs for anti-MERS-CoV activity in cell culture and found four (chloroquine, chlorpromazine, loperamide, and lopinavir) that were capable of inhibiting MERS-CoV replication at low micromolar concentrations. Further evaluation of these agents in animal models is recommended. In MERS-CoV-infected patients, administration of drugs such as these—even if not 100% effective in blocking viral replication—could provide a window of opportunity during which the patient's immune system might begin to respond to the infection (de Wilde, A.H. et al (2014)). A systematic review of drugs evaluated in preclinical and clinical studies against MERS-CoV found that the combination of lopinavir/ritonavir and interferon-beta-1b gave excellent results in common marmosets, and has progressed to testing in a randomized control trial setting. Ribavirin and interferon were the most widely used combination in observational studies, and may warrant further investigation (Momattin, H. et al (2019)).

Corticosteroids

Corticosteroids were widely used during the SARS epidemic although there was little consensus at the time regarding optimal treatment regimens. A review published some years later by Chinese researchers concluded that corticosteroid therapy had a positive impact on oxygenation index (OI), used as a measure of efficacy. Among the 225 SARS patients treated at a single Chinese center in 2003, the use of corticosteroids increased OI from an average of 237 mmHg at baseline to 335 mmHg after steroid administration. The optimum dose was determined to be 1-3 mg/kg (or 160-240 mg/day) for a total accumulated dose of 1000-2000 mg. The optimum duration of treatment was 8-14 days (Jia, W.D. et al (2009)).

Data obtained in a Hong Kong hospital support use of pulsed methylprednisolone as rescue therapy only during the later stages of SARS; administration during the earlier phases of disease appeared to actually prolong viremia (Hui, D.S. et al (2010)). In fact, a retrospective study of data on treatment of SARS patients during the epidemic shows that corticosteroids use was associated with worse outcomes (Stockman, L.J. et al (2006)), and as such they should be used only with caution in the treatment of patients with MERS (Zumla, A. et al (2015)). Based on this experience, routine use of corticosteroids is not recommended in patients with 2019-nCoV (Huang, C. et al., 2020).

Broad-Spectrum Antiviral Agents

Ribavirin is a ribonucleoside analogue that is active against some coronaviruses, as well as respiratory syncytial virus and metapneumoviruses. Because of its relatively broad spectrum of antiviral activity, ribavirin was one of the first compounds tested for its clinical efficacy against SARS. Early therapy with ribavirin, particularly when combined with corticosteroids, was used for the treatment of SARS patients, with variable results (Cleri, D.J. et al (2010)). Ribavirin has

also been tested in the rhesus macaque model of MERS-CoV, which is a model of mild to moderate human disease. The results obtained—IFN- α 2b plus ribavirin reduced virus replication, moderated the host response and improved clinical outcome—support use of the combination to treat patients with MERS (Falzarano, D. et al (2013)). However, a retrospective study of 20 patients in Saudi Arabia who received the combination therapy between October 2012 and May 2014 revealed that while 14-day survival improved significantly with ribavirin/IFN α -2a combination therapy as compared to standard of care, the difference no longer existed at 28 days (Omrani, A.S. et al (2014)). Adverse events, including dose-dependent anemia, arrhythmia, chest pain and dizziness, are a significant concern with ribavirin (Cleri, D.J. et al (2010)).

With the possible exception of ribavirin, there is a lack of broad-spectrum antiviral agents. Unlike other infectious agents (bacteria, fungi and parasites), viruses share extremely few common features that could be targeted by broad-spectrum agents. The development of broad-range agents requires a better understanding of pivotal virus-host interactions and the identification of targetable host cell proteins involved. German researchers have reported that the calcineurin/NF-AT pathway plays an important role in immune cell activation in CoV-infected hosts, and that non-immunosuppressive derivatives of ciclosporin may be capable of interrupting this process, thereby acting as broad-spectrum pan-CoV inhibitors (Pfefferle, S. et al (2011)).

Viral Enzyme Inhibitors

The process of coronavirus replication is well understood. Several unique steps have been identified as potential targets for antiviral drugs. Viral fusion with the host cell could potentially be blocked by entry inhibitors or membrane fusion inhibitors, similar to antivirals used for HIV infection. Viral protease inhibitors may block cleavage of the polymerase protein to inhibit viral RNA synthesis. Nucleoside inhibitors might specifically inhibit viral replication without causing damage to the host cell. Targeted inhibitors of the serine proteases, which are required to activate the viral infectivity of some coronaviruses, may block the later stages of the viral life cycle (Kilianski, A. et al (2014); Zhou, Y. et al (2015)); a number of host proteases have been shown to proteolytically process the S protein, which determines viral entry. These include cathepsin, furin and trypsin (Millet, J.K. et al (2015); Kilianski, A. et al (2014)). The S protein can also be activated by other host proteases including type II transmembrane serine protease (TMPRSS2), which is considered a promising antiviral drug target (Kilianski, A. et al (2014); Li, F. et al (2019)).

The protease inhibitor combination lopinavir/ritonavir has progressed furthest in development for treatment of MERS-CoV. Following successful preclinical evaluation of lopinavir/ritonavir plus interferon- β 1b, in which significant reductions in mortality were obtained in a marmoset model, clinical evaluation of the combination was recommended (Chan, J.F. et al (2015)). The ongoing MIRACLE trial is evaluating the efficacy and safety of lopinavir/ritonavir plus recombinant interferon- β 1b compared to placebo—both given in combination with optimal supportive care—in patients with laboratory-confirmed MERS-CoV infection requiring hospital admission (Arabi, Y.M. et al (2018)).

Since the combination of lopinavir and ritonavir was already available in the Wuhan, China hospital where early 2019-nCoV-infected patients were treated, a randomized controlled trial was quickly initiated to assess the efficacy and safety of the combination to treat this emerging coronavirus infection (Huang, C. et al., 2020).

Elements of the viral replication process have also been identified as potential therapeutic targets, including viral helicase, features of which are highly conserved among different coronaviruses (Adediji, A.O. et al (2014)). Other potential antiviral drug targets include virus assembly and exocytosis, which enables the release of virus from host cells. Despite a good understanding of viral targets and the identification of potential antiviral agents in vitro and in animal models, however, these findings have not translated into efficacy in humans (Zumla, A. et al (2016)).

Interferons

Investigators from Frankfurt University Medical School, Frankfurt, Germany, evaluated the antiviral activity of interferon-beta, interferon-alfa and interferon-gamma against SARS-CoV strains isolated from patients in Frankfurt and Hong Kong and replicated in Vero and Caco-2 cell lines (Hensley, L.E. et al (2004)). IFN-beta showed good antiviral activity, inhibiting SARS-CoV replication in both cell lines. IFN-alfa was also active, but with a sensitivity index 50-90 times lower than that for IFN-beta. IFN-gamma was slightly more active than IFN-alfa in one cell line but was completely inactive in the other (Cinatl, J. et al (2003)). In vitro, MERS-CoV has been shown to be 50-100 times more susceptible than SARS-CoV to treatment with interferon alfa (Abdel-Moneim, A.S. (2014)).

Canadian researchers described the use of combination therapy incorporating interferon alfacon-1 plus corticosteroids to treat a small group of patients diagnosed with probable SARS at a Toronto hospital between April 11 and May 30, 2003. Nine patients were given the combination therapy, while 13 patients were treated with corticosteroids alone. Both treatment strategies had similar effects on fever and leukopenia. However, the incidence of transfers to the intensive care unit and need for intubation and mechanical ventilation were lower in the interferon/corticosteroid combination group (33.3% and 11.1%, respectively) than in the corticosteroid monotherapy group (38.5% and 23.1%, respectively). Most significantly, the incidence of mortality in the corticosteroid therapy group was 7.7%, whereas there were no deaths in the combination therapy group. Furthermore, chest x-rays were normal within four days of initiating combination therapy, versus nine days in the corticosteroid monotherapy group (Loutfy, M.R. et al (2003)).

In early June 2003, Amarillo Bioscience announced that it would distribute its low-dose oral interferon alfa lozenges for the potential treatment and prevention of SARS in China and Taiwan. Low-dose oral interferon alfa significantly reduces mortality in piglets infected by the transmissible gastroenteritis coronavirus (TGEV) when administered once daily for four days, suggesting a possible benefit in SARS-infected humans.

A study demonstrated that Alferon N (interferon alfa-n3) had the most potent antiviral activity against the SARS-CoV among 19 clinically approved antiviral drugs of the major antiviral pharmacologic classes (Tan, E.L. et al (2004)).

Immunomodulators

During the SARS epidemic, the Chinese government granted approval for use of immune system enhancers such as SciClone's Zadaxin (thymosin alpha 1), an immune system enhancer that is marketed in China for hepatitis B, to treat patients with SARS. Zadaxin works by stimulating the production of white blood cells, enhancing the body's ability to fight off infection. Although there is no conclusive data available regarding the product's efficacy in the SARS indication, it is regarded by some as a promising therapy for this and other infectious disorders (Goldstein, A.L. et al (2009)).

Because ribavirin decreases the release of proinflammatory cytokines in mice infected with the mouse hepatitis coronaviruses, it may also act as an immunomodulator (Peiris, J.S. et al (2003)). In vitro studies indicate that ribavirin concentrations that inhibit other viruses are not sufficient to inhibit the replication of the SARS-CoV (Normile, D. (2003)). Therefore some of its benefits may be due to its immunomodulatory activity (Mazzulli, T. et al (2004)).

Other treatment options with immunomodulating properties were also used during the SARS epidemic, including i.v. immunoglobulins and convalescent-phase plasma (Tai, D.Y. (2007); Mair-Jenkins, J. et al (2015)).

During the MERS-CoV outbreak in 2015, some Korean patients were treated with convalescent plasma, i.e. passive immunotherapy entailing the infusion of blood plasma from patients who had overcome the infection. A systematic review and meta-analysis of healthcare databases and so-called grey literature describing the use of convalescent plasma, serum or hyperimmune immunoglobulin derived from convalescent plasma to treat severe acute respiratory infections of viral origin has concluded that this approach is safe and may decrease the risk of mortality

(Mair-Jenkins, J. et al (2015)). However, Saudi Arabian scientists reported that clinical trials evaluating this therapy would be challenging due to the limited availability of suitable donors, i.e. individuals with sufficiently high antibody titers (Arabi, Y. et al (2016)).

Monoclonal Antibodies

Monoclonal antibodies (MAbs) often represent the first line of investigation and defense against emerging diseases. Neutralizing MAbs, including murine, chimeric and fully human antibodies have been tested; the latter are preferred due to their reduced immunogenicity (Jin, Y. et al (2017)).

Scientists at the Dana-Farber Cancer Institute reported the isolation of an antibody from a human library capable of blocking infection of the SARS-CoV. The 80R antibody is targeted to the spike glycoprotein, and blocks the virus from binding to ACE2 receptors. The antibody was tested in animal models, in which it protected against acute lung injury. Such an antibody is envisioned for use in passive immunization for the early treatment of the SARS-CoV infection (Sui, J. et al (2004); Cleri, D.J. et al (2010)). However, subsequent studies showed that the antibody was not broadly protective, as it was ineffective against a distinct strain of SARS-CoV associated with the 2003/2004 outbreak (Cleri, D.J. et al (2010)).

Researchers from the National Cancer Institute later reported two new antibodies with improved affinity for the ACE2 receptor as compared to 80R. These MAbs, designated m396 and S230.15, were shown in modeling studies to be capable of neutralizing all SARS-CoV isolates from the two outbreaks in humans as well as strains isolated from palm civets; they may therefore be applicable to use in the diagnosis, prevention and/or treatment of future SARS infections (Zhu, Z. et al (2007)).

Neutralization of Middle East respiratory syndrome coronavirus has also been achieved using monoclonal antibodies. In a collaborative study by U.S. and Chinese researchers, three MAbs targeting the receptor (CD26/DPP4) binding domain of the MERS-CoV spike glycoprotein were identified from a large library of candidate antibodies and were evaluated in vitro. The MAb m336 neutralized the virus with exceptional potency, and was reported to have great potential as a candidate therapeutic or as a reagent to facilitate the development of MERS-CoV vaccines (Ying, T. et al (2014)). Japanese researchers have also investigated anti-CD26 MAb for MERS-CoV and have identified the humanized MAb YS110 as a promising candidate, with the advantage that this agent has already undergone clinical testing for other indications (Ohnuma, K. et al (2013)).

Current Coronavirus Pipeline

Consult the tables below for an overview of all products mentioned in this review, including drugs, biologics and diagnostic agents that have been marketed or are under active development for this indication. Tables may also include drugs not covered in the preceding sections because their mechanism of action is unknown or not well characterized.

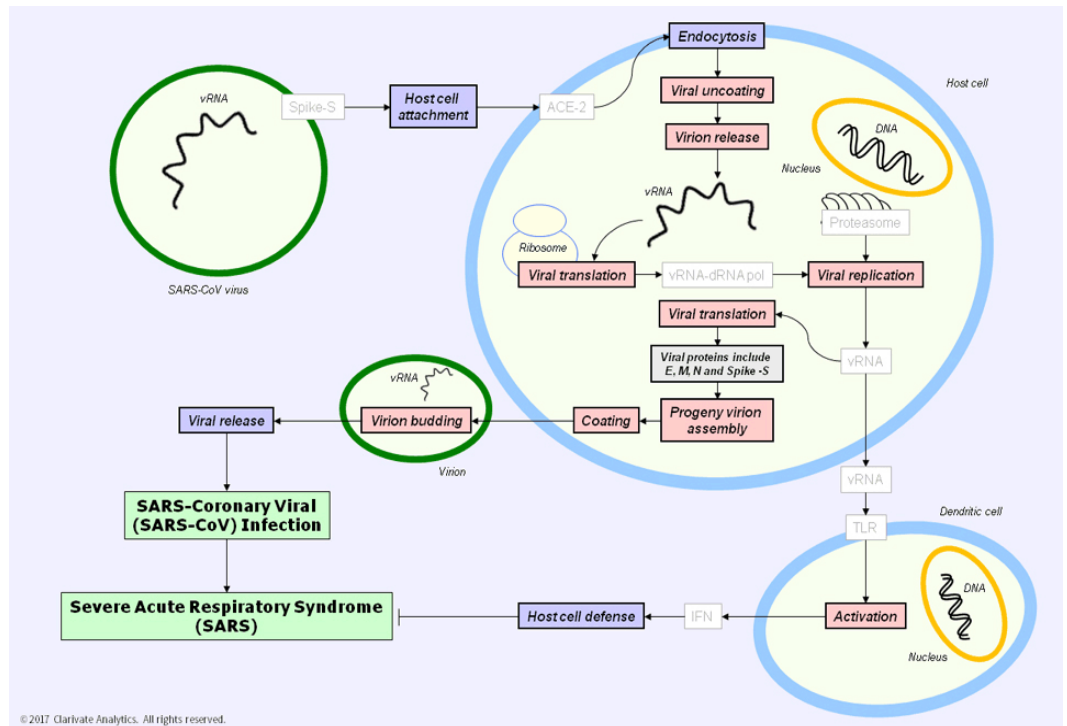
Drug	Organization	Description	Phase
Lopinavir/ritonavir	King Abdullah International Med Res Cent	Combination of lopinavir and ritonavir	Phase II/III
Convalescent plasma	King Abdullah International Med Res Cent	Plasma from patients who recently recovered from Middle East Respiratory Syndrome Corona virus (MERS - CoV)	Phase II
ChAdOx1 MERS	Vaccitech Ltd.; University of Oxford	Middle East respiratory syndrome recombinant (MERS) vaccine consisting of replication - deficient simian adenovirus vector ChAdOx1 carrying full - length spike gene of MERS - CoV camel isolate; under the control of human cytomegalovirus major immediate early promoter (IE CMV)	Phase I
MVA-MERS-S	Ludwig-Maximilians-Univ. Muenchen	Middle East respiratory syndrome coronavirus (MERS - CoV) vaccine comprising modified vaccinia virus encoding full - length S protein of MERS - CoV, under the control of early/late promoter PmH5	Phase I
REGN-3048	Regeneron	Human monoclonal IgG1 antibody targeting the S protein of Middle East respiratory syndrome coronavirus (MERS - CoV); produced in CHO cells	Phase I
REGN-3051	Regeneron	Human monoclonal IgG1 antibody targeting the S protein of Middle East respiratory syndrome coronavirus (MERS - CoV); produced in CHO cells	Phase I
SAB-301	SAB Biotherapeutics	Fully human polyclonal antibody targeting MERS - CoV spike (S) purified from transchromosomal cattle	Phase I
GNR-007	International Biotech Center Generium	Humanized monoclonal antibody IgG1K against epitope A of fusion protein (protein F) antigen of respiratory syncytial virus	Preclinical
GREVAX/MERS	Greffex	Recombinant adenoviral vector developed using GREVAX Universal Platform (GREVAX vector) encoding Middle East respiratory syndrome	Preclinical

coronavirus (MERS - CoV) antigens			
Human leukocyte interferon alpha	AIM ImmunoTech	Interferon alpha proteins comprising approximately 166 amino acids ranging in molecular weights from 16, 000 to 27, 000 daltons	Preclinical
LCA-60	Humabs BioMed	Human monoclonal antibody targeting coronavirus spike protein, produced in CHO cells	Preclinical
MVA-MERS-S_DF1	Universitaetsklinikum Hamburg-Eppendorf	Middle east respiratory syndrome (MERS) vaccine consisting of a modified vaccinia ankara (MVA) virus encoding MERS - CoV spike (S) protein antigens	Preclinical

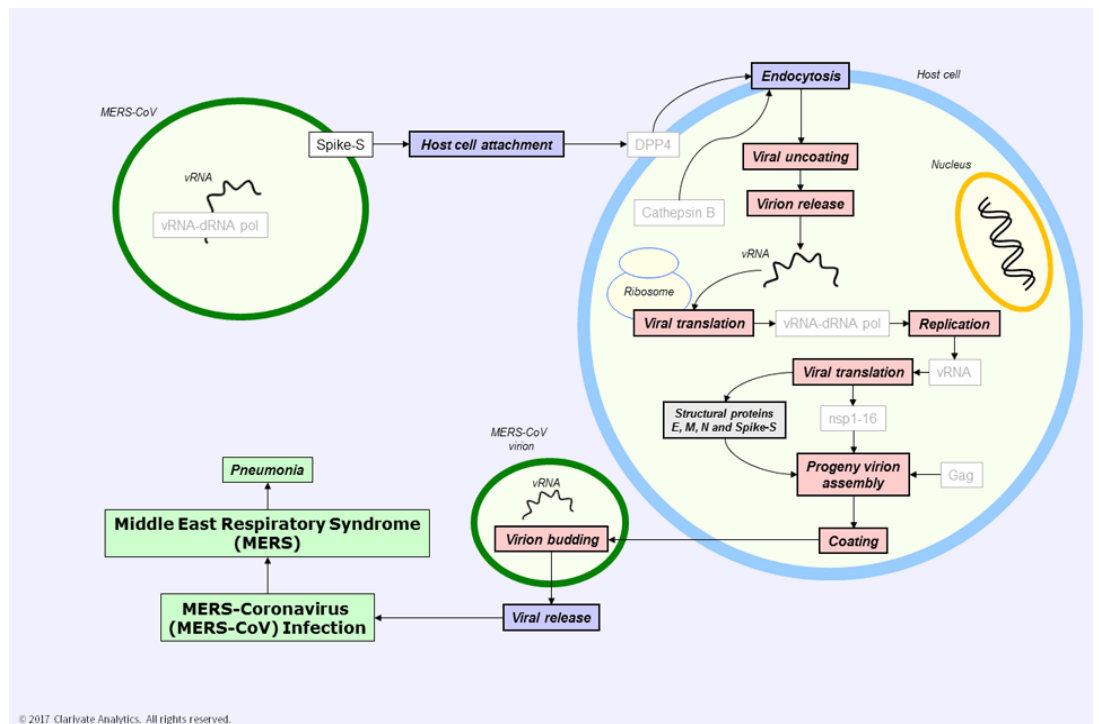
Targets for therapeutic intervention.

For an overview of validated therapeutic targets for this indication, consult the targetscape below. The targetscape shows an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of the condition and their biological actions. An arrow indicates a positive effect; a dash indicates a negative effect. Gray or lighter symbols are protein targets that are not validated (i.e., not under active development [UAD]). Pink text boxes with red borders indicate validated gene targets. Yellow text boxes are gene targets not UAD. Purple and pink text boxes indicate extracellular and intracellular effects, respectively. Green text boxes indicate a related disease/condition/symptom. For in-depth information on a specific target or mechanism of action, see the corresponding section in this report.

SARS-CoV Infection Targetscape



MERS-CoV Infection Targetscape



Latest Headlines

12-Aug-2019

Phase I safety and immunogenicity data for GLS-5300 MERS vaccine

Researchers from the Walter Reed Army Institute for Research and GeneOne Life Science presented results from a phase I study of the GLS-5300 Middle East respiratory syndrome (MERS) coronavirus DNA vaccine (ClinicalTrials.gov Identifier NCT02670187). At the time of data analysis, 75 healthy adult volunteers (aged 18 to 50 years) were enrolled in the open-label, single-arm, dose-escalation, phase I study, designed to evaluate the safety, tolerability and immunogenicity of the GLS-5300 MERS coronavirus DNA vaccine in healthy adults. Eligible participants were enrolled sequentially using a dose-escalation protocol to receive 0.67, 2 or 6 mg GLS-5300 administered by trained clinical site staff via a single intramuscular 1-mL injection at each vaccination at baseline, week 4 and week 12, followed immediately by colocalized intramuscular electroporation. Enrollment into the higher dose groups occurred after a safety monitoring committee reviewed the data following vaccination of the first 5 participants at the previous lower dose in each group. At the time of data cutoff, 25 subjects were enrolled in each of the 3 dose cohorts. No vaccine-associated serious adverse events (SAEs) were reported, with the most commonly reported AEs being injection-site reactions. Overall, 73 of 75 participants (97%) reported at least one solicited AE, with the most common systemic symptoms being headache and malaise or fatigue. The most commonly reported local solicited symptoms were administration site pain and tenderness, with most of these solicited symptoms being reported as mild and were self-limiting. Unsolicited symptoms were reported for 56 of the 75 participants (75%) and were deemed treatment-related for 26 participants (35%). The most common unsolicited AEs were infections, which occurred in 27 participants (36%), and 6 (8%) of these were deemed possibly related to study treatment. There were no laboratory abnormalities of grade 3 or higher that were related to study treatment. Laboratory abnormalities were generally uncommon, except for 15 increases in creatine phosphokinase, reported in 14 participants. Of these 15 increases, 5 (33%) were deemed possibly related to study treatment. Seroconversion measured by S1-ELISA occurred in 59 of 69 participants (86%) and 61 of 65 participants (94%) after two and three vaccinations, respectively, and neutralizing antibodies were detected in 34 of 68 participants (50%). T-cell responses were detected in 47 of 66 participants (71%) after two vaccinations and in 44 of 58 participants (76%) after three vaccinations. No differences in immune responses were seen between dose groups after 6 weeks. At week 60, vaccine-induced humoral and cellular responses were detected in 51 of 66 participants (77%) and 42 of 66 participants (64%), respectively. Taken together, these results support further development of the GLS-5300 vaccine, including additional studies to test the efficacy of GLS-5300 in a region endemic for MERS coronavirus (Modjarrad, K. et al. Lancet Infect Dis 2019, Advanced publication).

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29-Jun-2018

Inovio reports phase I results for INO-4700 in MERS

Inovio Pharmaceuticals has reported promising phase I results of its collaborative vaccine study with INO-4700 (GLS-5300) against Middle East respiratory syndrome (MERS) (ClinicalTrials.gov Identifier NCT02670187). Results for INO-4700, which is being codeveloped by Inovio and GeneOne Life Science, showed that the drug was well tolerated and demonstrated overall high levels of antibody responses in roughly 95% of subjects, while also generating broad-based T-cell responses in nearly 90% of study participants. The open-label, dose-escalation MERS vaccine trial, in partnership with the Walter Reed Army Institute of Research in Maryland, displayed antibody responses by ELISA in 94% of subjects at week 14 (2 weeks post-third dose). Additionally, there were no statistically significant dose-dependent differences in antibody response rates (91%, 95%, and 95% at doses of 0.67, 2, and 6 mg, respectively). Durable antibody responses to INO-4700 were also maintained through 60 weeks following dosing. In collaboration with GeneOne Life Science, Inovio plans to begin a phase I/II study for MERS in

the third quarter of this year. The study will be conducted by GeneOne Life Science in Korea and will be fully funded by a USD 34 million grant from the Samsung Foundation through the International Vaccine Institute. In April, Inovio was awarded USD 56 million to develop a MERS vaccine through phase II by The Coalition for Epidemic Preparedness Innovations (CEPI). Inovio and CEPI aim for the MERS vaccine to be available for stockpile as soon as possible for emergency use. The CEPI funding also included support for Inovio's vaccine against the Lassa virus (Inovio Pharmaceuticals News Release).

12-Apr-2018

University of Oxford initiates phase I trial of MERS-CoV vaccine

The University of Oxford, U.K., has initiated a phase I study to evaluate the safety and immunogenicity of a candidate Middle Eastern respiratory syndrome coronavirus (MERS-CoV) vaccine, ChAdOx1 MERS (ClinicalTrials.gov Identifier NCT03399578). The open-label trial will enroll 24 healthy volunteers, who will each receive three vaccinations in total with the experimental MERS vaccine. ChAdOx1 MERS will be administered intramuscularly alone as a single administration. There are three different vaccine schedules: Group 1 (n = 6) will receive 5 x 10⁹ vp ChAdOx1 MERS; Group 2 (n = 9) will receive 2.5 x 10¹⁰ vp ChAdOx1 MERS; and Group 3 (n = 9) will receive 5 x 10¹⁰ vp ChAdOx1 MERS. The study will assess the safety of the vaccine and immune responses to the vaccinations. The trial is expected to conclude next year (ClinicalTrials.gov Web site).

07-Mar-2018

Themis and CEPI partner on vaccines for Lassa fever and MERS

Themis Bioscience and the Coalition for Epidemic Preparedness Innovations (CEPI) have established a partnership under which Themis will provide advanced development and manufacturing for vaccines for Lassa fever and Middle East respiratory syndrome (MERS). This is the first company agreement that CEPI has signed since it was established last year as a coalition to finance and coordinate the development of new vaccines to prevent and contain infectious disease epidemics. The agreement will enable funding for Themis' development efforts over a 5-year period. Themis has established a versatile technology platform for the discovery, development and production of vaccines as well as other immune system activation approaches. The company will apply its platform technology to discoveries made by Institut Pasteur and the Paul Ehrlich Institut on Lassa fever and MERS, respectively, and will advance those vaccine candidates up to human proof-of-concept and safety studies (Themis Bioscience and the Coalition for Epidemic Preparedness Innovations News Release).

22-Feb-2018

NIAID initiates phase I study of MERS-CoV antibodies REGN-3048 and REGN-3051

The U.S. National Institute of Allergy and Infectious Diseases (NIAID) has initiated a phase I study to evaluate co-administration of two Middle East respiratory syndrome coronavirus (MERS-CoV) antibodies, REGN-3048 and REGN-3051 (ClinicalTrials.gov Identifier NCT03301090). REGN-3048 and REGN-3051 are both fully monoclonal antibodies that bind to the S protein of MERS-CoV. REGN-3051 can reduce virus titers and ameliorate MERS-CoV-induced lung pathology when given post infection. This first-in-human, single-site, randomized, double-blind, placebo-controlled study will evaluate the safety, tolerability, pharmacokinetics and immunogenicity of single ascending doses of a coadministered (1:1, w/w) combination of REGN-3048 and REGN-3051 monoclonal antibodies, administered intravenously in healthy adult volunteers. The 16-month study will enroll approximately 48 evaluable subjects, with 8 subjects in each one of six sequential ascending intravenous dose cohorts. REGN-3048 and REGN-3051 will be coadministered as single, ascending intravenous doses at 1.5, 5, 15, 25, 50 and 75 mg/kg of each (ClinicalTrials.gov Web site).

12-Jan-2018

Anti-MERS human antibody derived from transchromosomal cattle safe in phase I trial

A phase I study has been conducted in healthy volunteers to evaluate SAB-301, a human immune globulin G (IgG) polyclonal antibody targeting the Middle East respiratory syndrome (MERS)-CoV spike (S) protein purified from immunized transchromosomal cattle immunized with a MERS coronavirus vaccine. SAB Biotherapeutics is developing the product. A randomized, double-blind, phase I study evaluated SAB-301 doses of 1, 2.5, 5, 10, 20 and 50 mg/kg (n = 28) or placebo (n = 10) given on day 0 in healthy subjects (ClinicalTrials.gov Identifier NCT02788188). In SAB-301-treated patients, 64 adverse events were reported in 23 subjects, with a mean 2.3 per subject. There were 33 adverse events in placebo-treated subjects, with a mean 3.3 per subject. The most common adverse events were headache, albuminuria, increased creatine kinase, common cold, myalgia and low serum bicarbonate; hypotensive events, fatigue and loose stools, and sore throat occurred in more than 1 subject given SAB-301 and not in similar proportions to the placebo group. One serious adverse event, suicide attempt, occurred in a participant given SAB-301 at 50 mg/kg. SAB-301 exposure was slightly less than dose proportional. Mean t_{1/2} was approximately 28 days. Anti-MERS microneutralization titers correlated with serum SAB-301 concentrations. The highest tolerated dose in the study, 50 mg/kg, was recommended for initial use in human efficacy trials (Beigel, J.H. et al. Lancet Infect Dis 2018, Advanced publication).

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19-Sep-2017

Inovio Pharmaceuticals cleared to begin trial of MERS vaccine

Inovio Pharmaceuticals said the Korean Ministry of Food and Drug Safety approved the initiation of a study to evaluate GLS-5300, Inovio's vaccine against the Middle East respiratory syndrome (MERS) virus, in a phase I/IIa trial, to be conducted by partner GeneOne Life Science. The International Vaccine Institute is fully funding the trial via a USD 34 million grant that Samsung Foundation committed in 2015 to support the development of a MERS vaccine. The study is designed to assess the responses of GLS-5300 delivered intradermally. In preclinical challenge studies, GLS-5300 protected 100% of vaccinated rhesus macaques from a lethal MERS virus challenge (Inovio Pharmaceuticals News Release).

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23-Aug-2016

Regeneron Pharmaceuticals signs agreement with BARDA for MERS research

Regeneron Pharmaceuticals has signed an agreement with the Biomedical Advanced Research and Development Authority (BARDA) to manufacture and study two antibodies for the potential prevention and treatment of Middle East Respiratory Syndrome (MERS). The agreement includes funding of up to USD 8.9 million to support packaging and labeling of the antibodies for human use, the preparation and submission of an investigational new drug (IND) application with the FDA, and a National Institutes of Health (NIH)-conducted clinical trial in healthy volunteers. Currently there are no approved medicines or vaccines to treat or prevent MERS, which causes severe respiratory tract infections and is associated with high death rates (Regeneron Pharmaceuticals News Release).

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29-Jan-2016

Phase I study of MERS vaccine begins

Inovio Pharmaceuticals and GeneOne Life Science are recruiting for a collaborative phase I study of GLS-5300, an Inovio vaccine for Middle East respiratory syndrome (MERS) that the companies are codeveloping. The primary and secondary goals of the trial are to obtain safety and immunogenicity data. The trial, conducted in partnership with the Walter Reed Army Institute of Research, represents the first MERS vaccine to be tested in humans. Inovio and

GeneOne are also working on a preclinical vaccine for the emerging Zika virus (see Thomson Reuters Drug News, January 26, 2016).

23-Nov-2015

FDA clears first-in-human study of GeneOne and Inovio's MERS vaccine

The FDA has cleared the first-in-human study of a vaccine for Middle East respiratory syndrome (MERS) (GLS-5300) being codeveloped by GeneOne Life Science and Inovio Pharmaceuticals. The partners plan to initiate the first human trial of this MERS vaccine before the end of the year in partnership with the Walter Reed Army Institute of Research (WRAIR). The trial will be conducted at WRAIR under a joint clinical development agreement entered into earlier this month between GeneOne and WRAIR (GeneOne Life Science News Release).

Multimedia

- Glucocorticoid-Modulated Inflammation: Molecular Mechanisms Involved
- Immune Response
- MERS-CoV Infection Targetscape
- Novel Human Coronavirus: MERS-CoV
- Polymerase Chain Reaction (PCR)
- Pulmonary Fibrosis: Pathogenesis
- Respiratory System
- SARS Virus: Structure and Life Cycle
- SARS-CoV Infection Targetscape

Glossary

A

Acute

Referring to a health-related state or exposure that indicates brief (short-term) duration and strong intensity.

Adult Respiratory Distress Syndrome (ARDS)

See Acute Respiratory Distress Syndrome (ARDS)

AIDS

See Acquired Immune Deficiency Syndrome

Alveoli, Pulmonary

Thin-walled sac-like terminal dilations of the respiratory bronchioles where gas exchange occurs between alveolar air and pulmonary capillaries.

Analgesia

An insensitivity to pain.

Anemia

A condition characterized by too few circulating red blood cells resulting in insufficient oxygen to tissues and organs.

Anemia, Iron Deficiency

Iron deficiency anemia is one of the most common nutritional disorders and is due to excessive loss, deficient intake or poor absorption of iron. It is also known as nutritional hypochromic anemia. Iron is required for hemoglobin synthesis, which is responsible for the transport of oxygen in red blood cells. Red cells appear abnormal and are small (microcytic) and pale (hypochromic) in iron deficiency anemia.

Angiotensin Converting Enzyme (ACE)

An enzyme (EC 3.4.15.1) that cleaves the biologically inactive decapeptide angiotensin I to the active angiotensin II. High levels of ACE (normal values = 18-67 U/ml for individuals over age 20) are seen in sarcoidosis, histoplasmosis, alcoholic cirrhosis, asbestosis, berylliosis, diabetes, Hodgkin's disease, hyperthyroidism, amyloidosis, primary biliary cirrhosis, idiopathic pulmonary fibrosis, pulmonary embolism, scleroderma, silicosis, tuberculosis, Gaucher's disease and leprosy. See also Renin-Angiotensin System

Angiotensin Converting Enzyme 2 (ACE2)

A variant of the gene encoding ACE that is unlike the ubiquitously expressed ACE gene in that ACE2 is only expressed in cardiac, renal and testicular cells. The ACE2 protein has been shown to cleave angiotensin I and other vasoactive peptides. Modulators of ACE2 may be effective in the treatment of hypertension and congestive heart failure.

Angiotensin I

A biologically inactive decapeptide hormone that is formed in the circulation from the cleavage of angiotensinogen by renin. Angiotensin I is cleaved by angiotensin converting enzyme (ACE) resulting in the biologically active angiotensin II. See also Renin-Angiotensin System

Angiotensin II

The active form of angiotensin that is an octapeptide synthesized from angiotensin I and rapidly destroyed. It induces marked vasoconstriction resulting in an increase in blood pressure. It has other effects including stimulation of aldosterone release and renal absorption of sodium. See also Renin-Angiotensin System

Angiotensin II Receptors (AT1, AT2)

Receptor subtypes identified as AT1 and AT2. The G-protein-coupled AT1 receptor is responsible for the major physiological effects of angiotensin II. Agents targeting the AT1 receptor may be effective in the treatment of hypertension, heart failure and diabetic retinopathy. AT2 receptors have been localized in the rat brain, female reproductive organs and in neuronal tumor cells.

Angiotensinogen (AGT)

A polypeptide hormone (60 kD) that is an alpha-2 globulin and the substrate for renin. It is released from the liver and cleaved in the circulation by renin to form the biologically inactive decapeptide angiotensin I. Angiotensin I is then cleaved to the active angiotensin II by angiotensin converting enzyme (ACE). Angiotensin is broken down by angiotensinase. See also Renin-Angiotensin System

Anorexia

A condition characterized by an abnormal loss of appetite or an aversion to food. It can be caused by cancer, chemotherapeutics, AIDS, psychiatric disorder (i.e., anorexia nervosa) as well as other diseases.

Anorexia Nervosa

See Anorexia

Antibody

A protein synthesized by B lymphocytes in response to an antigen that has the ability to specifically bind with said antigen. Antibodies are the soluble form of the B cell's specific antigen receptors and are collectively referred to as immunoglobulins (Igs). Igs are produced in many different forms, each with different amino acid sequences and antigen binding sites. Through recruiting the complement system and various white blood cells, they protect the body by inactivating viruses and bacterial toxins and by killing invading microorganisms and larger parasites.

Antigen

Any molecule specifically recognized by B and/or T cells that can induce the formation of a specific antibody. For vaccines, the term antigen refers to a vaccine component that induces protection against a single disease.

Antigen Presenting Cells (APCs)

A heterogeneous population of leukocytes (i.e., Langerhans' cells, dendritic cells, B cells, etc.) with immunostimulatory properties, found predominately in skin, lymph nodes, spleen and thymus. APCs are capable of processing and presenting antigens to T cells in a class I or II restricted manner. APC function is dependent not only on surface expression of MHC I or II/antigen complexes, but also on costimulatory molecules (i.e., CD40 for B cells or CD28 for T cells) present on the surface of B cells, DCs, macrophages, endothelium and hemopoietic progenitors, which can provide a second activation signal in addition to the first signal of the antigen.

Antigenic

Having the properties of an antigen. Synonyms include immunogenic and allergenic.

Antigenic Drift

Minor changes in viral proteins (antigens) due to gene mutations within an influenza hemagglutinin or neuraminidase subtype.

Antigenic Shift

The sudden emergence of a new strain of influenza due to an abrupt change in the influenza hemagglutinin or neuraminidase protein type on the viral surface.

Antisense

Refers to the complementary strand of a coding sequence of DNA (antisense DNA) or mRNA (antisense RNA). These nucleotide sequences are not templates for synthesis but interact with complementary sequences in other molecules thereby affecting their function. Antisense therapy uses a DNA or RNA sequence that has the reverse orientation (i.e., opposite "sense"; antisense oligonucleotide) of the DNA or RNA sequence present in a specific disease-causing target gene and when administered, it will bind to the target gene and inhibit its expression. See also Antisense Oligonucleotide

Antisense Oligonucleotide

Complementary strands of small segments of mRNA that bind to specific mRNA sequences encoding for disease-causing proteins. Pairing of mRNA with antisense fragments blocks initiation of protein synthesis by reducing the availability of mRNA to ribosomes. Antisense oligonucleotides have been used to inhibit viral infections and to treat cancer and other diseases.

Apoptosis

An active form of cell death in which intrinsic cellular genetic programs are activated, leading to cellular suicide. Also known as programmed cell death.

ARDS

See Adult Respiratory Distress Syndrome (ARDS)

ATPase

An enzyme which causes the release of the terminal (gamma) phosphate from ATP yielding ADP and inorganic phosphate. Usually the enzymic activity is not just simple hydrolysis but rather a coupled system which is responsible for an energy-requiring process such as ion pumping (e.g., H⁺/K⁺-ATPase) or the generation of motility. See also H⁺/K⁺-ATPase

Autosomal Dominant

A genetic trait that is expressed when it is present as a single allele. Thus, only one affected parent is needed to pass it to offspring.

Autosomal Recessive

A genetic trait that is only expressed when it is present on both alleles of a gene. Thus, two chromosomes bearing the gene anomaly are required, one from each parent. The risk of transmitting an autosomal recessive disease is 1/4 (25%) at each pregnancy.

Autosome

A chromosome not involved in sex determination. The diploid human genome consists of 46 chromosomes: 22 pairs of autosomes in both males and females and 1 pair of sex chromosomes (XX in females and XY in males).

Axon

A single process (0.25 to more than 10 microns in diameter) of a neuron that conducts impulses away from the cell body and dendrites of that neuron. In contrast to dendrites, which are usually 1.5 mm in length, axons can reach up to 50 cm in length. Those axons that are 0.5 microns in diameter are usually encased in a myelin sheath. In the brain and spinal cord (CNS), oligodendroglia cells are responsible for the sheath, while Schwann cells make up the sheath in the peripheral nervous system. In general, axons transmit impulses to other nerve or effector cells via synaptic terminals.

B

B Cell

One of two major classes of lymphocytes that develop in adult bone marrow and in the fetal liver of mammals. B cells express surface immunoglobulins (Igs), which act as specific antigen receptors. Naive B cells (i.e., B cells that have never been activated) express variable levels of both IgM and IgD isotypes. With a few exceptions, B cell activation is dependent on both

recognition of a specific antigen and T cell help. Activated B cells divide and differentiate into either memory cells or plasma cells. Memory B cells are long-lived and express antigen receptors other than IgM or IgD; they have undergone rearrangements in their Ig genes that result in increased affinity for that particular antigen. Plasma cells are short-lived and secrete large amounts of Igs (i.e., the soluble form of the antigen receptor).

Bioavailability

The proportion of an administered drug absorbed into the bloodstream, indicating the physiological concentration of that drug.

Biomarker

Characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention.

Blind Trial, Single- or Double-

See Single-Blind and Double-Blind

Bronchitis

Inflammation of the airways (bronchi) which connect the trachea to the lungs. Acute bronchitis occurs suddenly and is resolved within a few days, while chronic bronchitis persists over a long period of time and may recur over several years.

Bronchus

One of two subdivisions of the trachea that conveys air to and from the lungs. Bronchi are lined with stratified ciliated columnar epithelium, possess a lamina propria and are composed of longitudinal networks of elastic fibers. Spirally arranged bundles of smooth muscle are also present in addition to irregular plates of hyalin cartilage in the outer wall.

C

Calcineurin

Calcineurin, also known as protein phosphatase 2B (PP2B; EC 3.1.3.16) is a calcium/calmodulin-dependent serine-threonine phosphatase that is composed of a catalytic subunit (A) and a regulatory subunit (B). There are three types of A subunits and two types of B subunits encoded by different genes. Calcineurin is essential for T cell activation since it dephosphorylates/activates the NF-AT transcription factor, which controls the expression of genes implicated in T cell activation. Calcineurin has been implicated in a wide variety of biological responses including lymphocyte activation, neuronal and muscle development, neurite outgrowth and morphogenesis of vertebrate heart valves. It has also been shown to have important roles in axonal guidance as well as memory and learning and plays a critical role in Ca^{2+} signaling and stress responses. When a macrophage or a dendritic cell interacts with a T cell receptor (TCR), there is an increase in the calcium levels, which in turn activates calcineurin, by binding to its regulatory subunit and activating calmodulin binding. Calcineurin induces different NF-ATs that are important in the transcription of several genes encoding proinflammatory modulators. Blocking the calcineurin action would inhibit T-cell activation thus blocking transcription of these genes. Ultimately, the production of proinflammatory modulators such as interleukins, interferon gamma (IFN γ) and tumor necrosis factor-alpha (TNF- α) would be decreased and the inflammatory response diminished. Inhibition of calcineurin signaling may be an effective therapeutic strategy for several autoimmune disorders such as graft-versus-host disease (GVHD).

cAMP (cyclic 3',5'-Adenosine Monophosphate)

The 3', 5' cyclic ester of adenosine monophosphate (AMP) which acts as a second messenger in signal transduction pathways. cAMP is generated from adenosine 5'-triphosphate (ATP) by the action of adenylate cyclase which is coupled to hormone receptors by G proteins. cAMP activates a specific protein kinase and is inactivated by phosphodiesterase forming 5' AMP. cAMP is responsible for smooth muscle relaxation during bronchodilation, increased ciliary beat frequency and decreased mucus viscosity.

Cancer

The abnormal, rapid, unorganized and uncontrolled proliferation of new tissue. The malignant tissue develops from a single cell that has undergone mutations in its DNA. This cell does not mature normally and eventually die but it divides prolifically. There are approximately 200 different types of cancers. Cancers arising from epithelial cells are called carcinomas and those arising from mesenchymal tissues are called sarcomas. Leukemias are also classified as malignant growths. Cancer cells can invade nearby tissues (i.e., metastasis) and can spread through the bloodstream and lymphatic system to other parts of the body.

Cathepsin L

A lysosomal cysteine proteinase (EC 3.4.22.15) thought to be involved in osteoclast-mediated bone resorption. Together with cathepsin B it activates caspase 3. Inhibition of this cathepsin may be effective in the treatment of neuronal injury due to ischemic stroke and COPD.

cccDNA

Covalently closed circular deoxyribonucleic acid.

CD3 (T Cell Receptor Complex)

The CD3 antigen is a protein complex composed of four distinct chains: CD3gamma chain, CD3delta chain and two CD3epsilon chains. These chains are highly homologous cell surface proteins that are members of the immunoglobulin superfamily and contain a single extracellular immunoglobulin domain. The transmembrane region of these CD3 chains is negatively charged allowing them to associate with the positively charged T cell antigen receptor (TCR) chains (TCRalpha and TCRbeta). The intracellular tails of the CD3 chains contain a single conserved motif known as an immunoreceptor tyrosine-based activation motif (ITAM) which is essential for the signaling capacity of the TCR. Association of the CD3 chains with TCR and the zeta-chain (accessory molecules of TCR) generates an activation signal in T lymphocytes. Thus, the TCR complex is composed of the TCR, zeta-chain and CD3 molecules. CD3+ T cells are increased in patients with Crohn's disease. Therefore modulation of the CD3 complex on T cells may be beneficial in the treatment of the disease.

CD4

CD4 (cluster of differentiation 4) is a transmembrane glycoprotein and member of the immunoglobulin (Ig) superfamily of receptors that is expressed on the surface of T helper (Th) cells, regulatory T cells, monocytes, macrophages and dendritic cells. It is a coreceptor that together with the T cell receptor (TCR) activates the T cell following interaction with MHC class II molecules present on the surface of antigen presenting cells. CD4 amplifies the signal generated by the TCR by recruiting the tyrosine kinase Lck. It has four Ig domains (D1-D4) exposed on the extracellular surface of the cell and uses the D1 domain to interact with the beta2-domain of MHC class II molecules. T cells expressing CD4 molecules (not CD8) on their surface are MHC class II-restricted, specific for antigens presented by MHC II and not by MHC class I. CD4 is a primary receptor used by HIV-1 to gain entry into host T cells. In multiple sclerosis (MS), myelin antigen-specific CD4+ T cells become activated in the peripheral immune compartment and cross the blood-brain barrier to trigger the disease. Commitment of T cells to proinflammatory effector T helper cell lineages (e.g., IL-17-producing CD4+ T cells or Th17 cells) appears to be an important inducer of organ-specific autoimmunity and studies suggest that Th17 cells are the dominant pathogenic cellular component in MS and other autoimmune inflammatory diseases. Decreasing myelin-specific CD4+ T cell responses with an anti-CD4 antibody, for example, could reduce demyelination and decrease immune cell infiltration into the CNS and thus, reduce subsequent initiation and progression of the autoimmune response. See also CD4+ T Cells

CD4+ T Cells

T cells expressing both the T cell antigen receptor-2 (alpha beta; TCR-2) and the CD4 marker. The TCR recognizes the antigen associated with major histocompatibility complex (MHC) on the surface of the antigen presenting cell (APC), while the CD4 molecule recognizes the class II MHC molecule only. Therefore, CD4 determines that a given T cell be class II- rather than class I-

restricted. CD4 also contributes to T cell activation by providing biochemical signals to the T cell at the time of antigen presentation. CD4+ cells can be subdivided into Th0, Th1, Th2 or Th3 populations, depending upon the cytokine profile they secrete. CD4+ cells have been implicated in the development and progression of rheumatoid arthritis. See also CD4

cDNA

See Complementary DNA (cDNA)

Central Nervous System (CNS)

The portion of the nervous system encompassing the brain and spinal cord.

Chemokine CXCR2 Receptor

See Interleukin 8 (IL-8) beta Receptor

Chemokine Receptors

G-protein-linked, 7-transmembrane (i.e., serpentine) receptors that bind chemokines and are used as coreceptors for the binding of immunodeficiency viruses (HIV, SIV, FIV) to leukocytes. Individuals deficient in particular CCRs seem to be resistant to HIV-1 infection. CXCR4 is a coreceptor for T-tropic viruses. CCR5 is the receptor for MIP-1alpha, MIP-1beta and RANTES and a primary coreceptor with CR4 for cell entry of macrophage-tropic HIV-1 strains. CCR5 is also implicated in asthma, rheumatoid arthritis and multiple sclerosis. Antagonists to the CCR1 (binds MIP-1alpha, RANTES, MIP-5/HCC-2), CCR2 (binds MCP-1, MCP-3, MCP-4) and CCR3 (binds, RANTES, MCP-2, MCP-3, MCP-4, eotaxin, MIP-5/HCC-2) receptors are under development for treatment of rheumatoid arthritis.

Chemokines

A large group of small polypeptide cytokines (e.g., IL-8, PF4, MCP-1, MIP-1alpha, RANTES) with proinflammatory activities synthesized by several cell types (e.g., monocytes, macrophages, T cells, mast cells, fibroblasts, endothelial cells, platelets, epithelium, microglial cells, keratinocytes). These molecules display a certain degree of selectivity for various immune cell types and are involved in activation of leukocytes during transendothelial migration and chemotaxis in tissues. The chemokine family is composed of two main subgroups: CC chemokines which contain two adjacent cysteine residues and CXC chemokines in which the two cysteine residues are separated by another amino acid. CXC chemokines are further subdivided into ELR+ or ELR- chemokines, where ELR indicates the amino acids (Glu-Leu-Arg) preceding the first cysteine residue. ELR+ chemokines are chemotactic for neutrophils and ELR- chemokines are chemotactic for lymphocytes.

Chimera

An organism made up of two genetically distinct cell types. It is created by fusing two early blastula stage embryos, by reconstituting bone marrow in an irradiated recipient or by somatic segregation.

Chlamydia

A genus of prokaryotes that replicate in cytoplasmic vacuoles within susceptible eukaryotic cells. *Chlamydia trachomatis* causes trachoma in man. Other species of *Chlamydia* can cause a variety of infections including urethritis, epididymitis and proctitis in men, cervicitis, salpingitis and acute urethral syndrome in women and conjunctivitis and pneumonia in newborn infants.

Chlamydia pneumoniae

A bacteria belonging to the Chlamydiaceae family that causes pneumonia and diseases of the upper and lower respiratory tract (e.g., pharyngitis, bronchitis and pneumonia). It has recently been associated with coronary heart disease and Alzheimer's disease (AD). The bacterium was detected in AD brains and related to tau-associated neurofibrillary pathology. Persistent *Chlamydia pneumoniae* infections are thought to instigate or complicate the inflammatory response leading to atherosclerosis and/or angina pectoris.

Chronic

A term referring to a health-related state or exposure that signifies prolonged (long-term) duration. In some instances, it can indicate low intensity.

Complementary DNA (cDNA)

Deoxyribonucleic Acid (DNA) synthesized a mature (i.e., fully spliced) mRNA template in a reaction catalyzed by reverse transcriptase (RT). RT acts on a single strand of mRNA yielding a sequence of DNA that complements the mRNA template; this strand of DNA is cDNA and can be used to clone eukaryotic genes in prokaryotes. RT generates its cDNA based on the pairing of RNA base pairs (A, U, G and C) to their DNA complements (T, A, C and G respectively).

Consolidation

The solidification into a firm dense mass as in inflammatory induration of a normally aerated lung due to the presence of cellular exudate in the pulmonary alveoli.

Coronaviridae

A family of medium sized single-stranded RNA viruses some of which are responsible for upper respiratory diseases while other cause animal infections (e.g., avian bronchitis, swine encephalitis, mouse hepatitis). The outer envelope of the virus has club shaped projections that radiate outwards and give a characteristic corona appearance to negatively stained virions. Coronavirus is the only genus.

Corticosteroids

A class of steroid hormones that are produced in the adrenal cortex and are involved in many physiologic processes including among others stress responses, immune responses, inflammation, carbohydrate metabolism, protein catabolism, electrolyte homeostasis and behavior. The class includes both glucocorticoids and mineralocorticoids although corticosteroid is often used synonymously for glucocorticoid. Corticosterone, cortisone and aldosterone are common endogenous corticosteroids. Corticosteroids have been shown to be effective for a number of indications including cancer, asthma, allergic rhinitis, rheumatoid arthritis, nausea, COPD and inflammatory bowel disease.

Coryza

A runny nose (also known as rhinorrhea). The word is thought to originate from the Greek "koryza" which means boiling over from the head. Coryzavirus is the former name for rhinovirus. See also Rhinorrhea

Creatine

An amino acid that is found in muscle but does not occur in proteins. Phosphorylated creatine (creatine phosphate or phosphocreatine) is the energy source for muscle contraction.

Creatine Kinase

A dimeric enzyme (82 kD; EC 2.7.3.2) that catalyzes the formation of ATP from ADP and creatine phosphate in muscle.

Creatinine

A waste product of protein metabolism found in the urine. Measurement of creatinine levels can indicate overall kidney function (i.e., high levels signify kidney dysfunction or failure).

Crossover Trial

A clinical study in which subjects receive two or more drugs separated by drug-free periods.

Cytokines

Soluble proteins produced by one of several cell types (i.e., T cells, B cells, fibroblasts, macrophages, epithelial cells, astrocytes, endothelium, monocytes) that are involved in signaling between cells of the immune system. Cytokines include interleukins, tumor necrosis factors (TNFs) and colony-stimulating factors (CSFs).

D

DALYs

Acronym for "Disability Adjusted Life Years" which is the sum of years of life lost due to premature death and the years lost due to living with disability. DALYs are used to assess the magnitude of disease, health risks, and premature death. DALYs for a disease or health condition are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences. $DALY = YLL + YLD$.

Deoxyribonucleic Acid (DNA)

A nucleic acid which contains deoxyribose as the sugar component loosely bound to protein. It stores the hereditary information required for cell growth and reproduction. It is a linear macromolecular chain of deoxyribose molecules esterified with phosphate groups between 3' and 5' hydroxyl groups. Purines (i.e., adenosine [A] and guanine [G]) and pyrimidines (cytosine [C] and thymine [T]) are linked to this structure. DNA is found in the nuclei (chromatin, chromosomes) and mitochondria of organisms. DNA is the autoreproducing component of viruses and contains all hereditary information. It may be open-ended or circular (e.g., mitochondrial DNA) and single- or double-stranded (e.g., chromosomes).

Diabetes Mellitus

A group of metabolic diseases characterized by chronic hyperglycemia with disturbances in carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. See also Diabetes Mellitus, Type 1 and Diabetes Mellitus, Type 2

Diacylglycerol (DAG)

A glycerol substituted on the 1 and 2 hydroxyl groups with long chain fatty acyl residues. It is a normal intermediate in the biosynthesis of phosphatidyl phospholipids and is released by phospholipase C (PLC). DAG is involved in signal transduction. Increased DAG levels in membranes activate protein kinase C (PKC). The high levels of glucose seen in diabetes increase the synthesis of DAG and PKC in vascular tissue. This can result in structural and functional abnormalities including changes in vascular permeability and gene expression in the retina (i.e., retinopathy) and kidney (i.e., nephropathy).

Diarrhea

A symptom characterized by loose or unformed stools, frequently accompanied by other gastrointestinal symptoms. It is nearly always a symptom of another disease or condition, rather than a disease in its own right. It is considered acute when it lasts for less than 4 weeks (typically associated with a bacterial or viral infection) and chronic when it persists for more than four weeks. Diarrhea is broadly classified as secretory, osmotic or exudative. Secretory diarrhea is caused by an increase in active secretion or an inhibition of absorption. Osmotic diarrhea occurs when too much water is drawn into the bowels. This can be the result of maldigestion (e.g., pancreatic disease or celiac disease), in which the nutrients are left in the lumen to pull in water, lactose or fructose intolerance, or use of osmotic laxatives, among other causes. Exudative diarrhea is characterized by the presence of blood and/or pus in the stool. This typically occurs with inflammatory bowel disease (Crohn's disease or ulcerative colitis) and severe infections.

Dipeptidyl Peptidase IV (DPP IV)

An enzyme (EC 3.4.14.5) that removes N-terminal dipeptides from peptide hormones of the GRF superfamily, including GIP, GLP-1, GLP-2, glucagon, VIP and NPY. DPP IV plays a catalytic role in the processes of signal transduction during immune responses leading to type 2 diabetes. Inhibition of DPP IV is thought to improve glucose tolerance by rescuing intact versions of the incretins GLP-1 and GIP, or by preventing their degradation.

DNA

See Deoxyribonucleic Acid (DNA)

Double-Blind

A research testing method characteristic of a controlled experiment/trial in which neither the participants nor the person administering the treatment know which treatment any particular subject is receiving. Usually the comparison is between an experimental drug and a placebo or a standard comparison agent.

Double-Dummy

A research testing method in which patients in all treatment groups receive medication of the same appearance, one of which is inactive (placebo) and the other active. For example, all patients would receive a topical cream and capsules. Those receiving the active cream received dummy capsules and vice versa.

Downstream

Segments of nucleotide sequences of DNA or RNA that are remote from the initiation sites (i.e., codons) and are transcribed or translated later. It is also used to describe events that occur late within sequential reactions. See also Upstream

Dysplasia

Pathological abnormality of development such as an alteration in size, shape and organization of adult cells.

Dyspnea

Shortness of breath and labored breathing.

E

Effectiveness

The therapeutic effect of an intervention as demonstrated or observed in the real-world setting. See also Efficacy

Efficacy

The therapeutic effect of an intervention as demonstrated or observed in a controlled setting, such as a clinical trial. See also Effectiveness

Emesis

Emesis is the complex reflex consisting of ejecting the contents of the stomach through the mouth. Also known as vomiting, this reflex can be triggered by various endogenous or exogenous factors.

Endocrine

A term referring to internal, ductless, secretion (i.e., into the systemic circulation) or to the glands or the hormones which secrete or are secreted, respectively, in this manner.

Endogenous

Originating from within an organism, tissue or cell.

Epidemic

Widespread high occurrence of a disease in a population or area.

Epithelium

The cellular avascular tissue layer that covers all free cutaneous, mucous and serous surfaces.

Etiology

The cause or origin of a disease.

Exacerbation

An increase in the severity of a disease or in any of its symptoms.

Exogenous

Originating from outside an organism, tissue or cell.

Exon

A sequence of DNA that encodes information for protein synthesis that is transcribed to messenger RNA.

F

Familial

An inherited disorder or trait.

Fibrosis

Formation of fibrous tissue in response to injury.

Fomite

Any inanimate object contaminated with a viable pathogen (e.g., bacterium, virus, etc.) that can transfer the pathogen to a host.

G

G-Protein

One of several mediators of activated cell surface receptors and their enzymes and ion channels. They are responsible for the signal transduction pathways which alter the concentration of intracellular second messengers (e.g., cAMP, cGMP, Ca²⁺). These second messengers in turn regulate the behavior of other intracellular target proteins, leading to the desired cellular response.

G-Protein-Coupled Receptor

Cell surface receptors that are coupled to G proteins (i.e., GTP binding protein). They have seven membrane spanning domains and have been divided into two subclasses: those in which the binding site is in the extracellular domain (e.g., receptors for glycoprotein hormones such as TSH and FSH) and those in which the ligand binding site is in the plane of the seven transmembrane domains (e.g., rhodopsin, receptors for small neurotransmitters and hormones such as the muscarinic acetylcholine receptor). Also called 7TM receptors.

Genome

The entire collection of genes and other functional and nonfunctional DNA sequences in the nucleus of an organism. It includes those genes that encode mRNAs, rRNAs, tRNAs and sn/scRNA and the functional sequences that occur as regulatory elements or as sites where replication begins. Much of the nonfunctional DNA consists of sequence elements repeated thousands or millions of times. Arrangement of functional and nonfunctional DNA within the genome is not fixed and existing sequences may be internally rearranged, moving from one location to another.

Genotype

The genetic constitution of an organism or cell.

Glucocorticoid Receptor (GR)

A nuclear receptor of the NR3 class also known as type II glucocorticoid receptor (GR), which exists as a dimer coupled with chaperone molecules (e.g., HSP90, HSP65). Chaperone molecules are shed subsequent to ligand binding. GR binds cortisol and corticosterone and also aldosterone and deoxycortisone but with less affinity. The activated receptor then binds nuclear hormone response elements and also affects transcription via protein-protein interactions with other transcription factors such as activator protein-1 (AP-1) and nuclear factor kappaB (NF-kappaB). Activation can result in potent anti-inflammatory activity as well as regulation of several cardiovascular, metabolic, immunologic and homeostatic responses. Synthetic glucocorticoid receptor ligands may be effective as a treatment for arthritis, dermatitis, allergic reactions, allergic rhinitis, atopic dermatitis, asthma, COPD, hepatitis, lupus erythematosus, inflammatory bowel disease, sarcoidosis, Alzheimer's-type dementia, and for glucocorticoid replacement in Addison's disease or other forms of adrenal insufficiency. On the other hand, GR antagonists

may be effective in the treatment for disorders involving pathological exposure to glucocorticoids such as Cushing's syndrome. These agents would reduce the effects of excess cortisol.

Glucocorticoids

A family of steroid hormones generally synthesized and secreted by the adrenal medulla which affect intermediary metabolism such as hepatic glycogen deposition. Glucocorticoids also have potent antiinflammatory activity. Glucocorticoid receptors are found in the cells of almost all vertebrate tissues.

Cortisol (also known as hydrocortisone) is the most potent naturally occurring hormone in this class. It regulates several cardiovascular, metabolic, immunologic and homeostatic responses. Synthetic glucocorticoids have been shown to be effective as a treatment for arthritis, dermatitis, allergic reactions, asthma, hepatitis, lupus erythematosus, inflammatory bowel disease, sarcoidosis and for glucocorticoid replacement in Addison's disease or other forms of adrenal insufficiency.

H

H⁺/K⁺ ATPase

An enzyme (hydrogen/potassium adenosine triphosphatase; EC 3.6.3.10) isolated from gastric mucosa that catalyzes the hydrolysis of ATP coupled with the exchange of hydrogen and potassium ions across the cell wall. See also ATPase

Half-life

The time required for one-half of an amount of a substance to be lost through biological processes.

Headache

Diffuse pain experienced in various regions of the head, not limited to the area of distribution of any single nerve.

Helicase

An enzyme that moves along the DNA template double helix, in front of DNA polymerase, separating the two chains. Also known as the unwinding enzyme. Once unwound, the nucleotide chains are stabilized by DNA binding proteins (e.g., helix destabilizing proteins or single-strand binding proteins) that bind to the chains and prevent rewinding in the region just behind the replication fork.

Hemagglutinin

A membrane glycoprotein (550 amino acids) of the influenza virus type A involved in receptor binding and fusion. The name is derived from its capacity to agglutinate red blood cells at neutral pH. There are 15 hemagglutinin (H) subtypes of which only 3 (H1, H2 and H3) are associated with human illness. No H subtypes have been identified for influenza B or C viruses.

Hemorrhage

Bleeding that classified according size (e.g., petechiae, very small; purpura, up to 1 cm; and ecchymoses, larger). Accumulation of blood within a tissue is known as a hematoma.

Hepatitis

An inflammatory liver disease. See also Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis E and Hepatitis D.

Hepatitis A

A form of viral hepatitis that is known as infectious hepatitis because it can spread through contact with oral secretions or stool or through sexual contact. See also Hepatitis A Virus

Hepatitis A Virus (HAV)

A small (27 nm diameter) single stranded RNA virus with some resemblance to enteroviruses (e.g., poliovirus) that is a member of the Picornaviridae family. It replicates in hepatocytes and is transmitted via the oral-fecal route. It can also be sexually transmitted.

Hepatitis B

An inflammatory process in the liver caused by the hepatitis B virus (HBV) that is characterized by patchy hepatocellular necrosis affecting all acini. Liver disease caused by chronic hepatitis B can be fatal due to the development of cirrhosis leading to liver failure and an increased risk of hepatocellular liver cancer.

Hepatitis B Surface Antigen (HBsAg)

HBV surface antigen (HBsAg) is associated with the viral surface coat and several subtypes have been identified. Detection of HBsAg in serum usually provides initial evidence of acute HBV infection. In general, HBsAg appears during the incubation period, 1 to 6 weeks prior to development of clinical or biochemical illness and disappears during convalescence. Corresponding antibody (anti-HBs) appears weeks or months later after clinical recovery and usually persists for life. Occasionally, HBsAg persists after infection and anti-HBs do not develop. These patients usually develop chronic hepatitis or become asymptomatic carriers of the virus.

Hepatitis B Virus (HBV)

A small enveloped DNA virus belonging to the Hepadnaviridae family. The infective particle of HBV consists of an inner core and an outer surface coat. The inner core contains double-stranded DNA and DNA polymerase which replicates in the nuclei of infected hepatocytes. The surface coat is added on in the cytoplasm and, for unknown reasons, is produced in large quantities. It is the surface coat which can be detected in serum as HBsAg.

Hepatitis C

An inflammatory process in the liver caused by the hepatitis C virus (HCV). Symptoms of hepatitis C may not manifest until the chronic stage and include jaundice, fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting. Cirrhosis from hepatitis C is the major condition responsible for the majority of orthotopic liver transplants in the U.S. Infection with hepatitis C has also been associated with increased risk of primary hepatocellular carcinoma.

Hepatitis C Virus (HCV)

An enveloped 9.5 kb positive strand RNA virus belonging to the Flaviviridae family. The virion consists of a nucleocapsid core and two envelope proteins within the lipid bilayer. Six nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B) are involved in viral replication, transcription and polyprotein processing. The virus mutates rapidly: at least six major HCV genotypes and more than 50 subtypes or quasispecies have been isolated.

Hepatitis, Fulminant

A rare syndrome usually associated with hepatitis B and, in rare cases, with hepatitis A or E. It is characterized by rapid clinical deterioration and the onset of hepatic encephalopathy. The liver parenchyma undergoes massive necrosis and the organ size decreases significantly. Hepatocellular failure and intravascular coagulation may cause bleeding. Functional renal failure sometimes occurs; in some cases, coma may develop within hours of onset.

Herd Immunity

The indirect protection of unvaccinated individuals against a given disease achieved via immunity of a sufficiently large proportion of the surrounding population against the respective pathogen, e.g., through vaccination or other methods of blocking transmission.

HIV

See Human Immunodeficiency Virus (HIV)

Human Immunodeficiency Virus (HIV)

A type of retrovirus first identified in 1983 that belongs to the Retroviridae family and genus lentivirus. HIV causes acquired immunodeficiency syndrome (AIDS) which involves a gradual

deterioration of the immune system resulting in opportunistic infections and eventual death. The virus is spread via sexual contact with an infected individual, exposure to contaminated blood (i.e., shared needles/syringes, infusions) and during pregnancy, delivery and/or through breast milk. Two HIV strains have been identified: HIV-1 the retrovirus that causes AIDS and is found worldwide and HIV-2, a virus closely related to HIV-1 that is less virulent, most common in West Africa and also causes immune system suppression. The two viruses differ in protein composition. For example, HIV-2 contains an additional accessory protein Vpx while lacking others. See also AIDS (Acquired Immune Deficiency Syndrome)

Hyaline

Refers to something that is clear, transparent, colorless and granule-free. Examples are hyaline cartilage and hyaline hyphae present in fungus such as *Aspergillus* spp.

I

Immune System

An integrated group of various cell types and the soluble molecules they secrete (i.e., antibodies, cytokines) responsible for immunity.

Immunization

The means to produce a protective immune response in susceptible individuals by administration of a living modified agent (e.g., yellow fever vaccine), a suspension of killed organisms (e.g., pertussis vaccine) or an inactivated toxin (e.g., tetanus). Immunization can be passive or active.

Immunization, Active

The means by which antibody production or cell-mediated immunity is stimulated by giving the antigen in the form of a vaccine or through exposure to naturally occurring antigens such as bacteria, viruses or fungi.

Immunization, Passive

A means to produce a temporary immune response against an infectious agent or toxin by giving preformed antibodies actively produced in another person or animal in the form of serum or gamma globulin.

Immunocompromised

Used to describe persons with an underdeveloped (as in the very young) or impaired immune system. The impairment may be a natural deterioration from age, or may be caused by disease or by the administration of immunosuppressive drugs.

Immunogen

An antigen that can induce antibody production.

Immunogenic

See Antigenic

Immunoglobulin (Ig)

A subgroup of globulins that are classified as alpha, beta and gamma according to lipid or carbohydrate content and physiological function. Antibodies are Igs and all Igs may function as antibodies. Serum Igs belong to the gamma group and constitute a family of glycoproteins that bind antigens. Serum Igs can be precipitated from plasma or serum and can be normal or specific. Serum Igs are classified into 5 groups: IgG, IgD, IgE, IgA and IgM.

Immunoglobulin A (IgA)

Major class of immunoglobulins found in mammalian serum, body fluids (i.e., tears and saliva) and in the respiratory, reproductive, urinary and gastrointestinal tracts. It protects the body's mucosal surfaces from infection. It is present in human colostrum but cannot be transferred across the placenta.

Immunoglobulin E (IgE)

IgE is a class of immunoglobulins or "antibodies" that attach to mast cells in the respiratory and intestinal tracts, triggering release of inflammatory modulators and resulting in manifestation of symptoms associated with allergic reactions. Of the five types of Igs (IgM, IgG, IgA, IgE and IgD) in the body, only IgE has been shown to be involved in allergic reactions. It is responsible for the symptoms seen in patients with allergic rhinitis, asthma and eczema. IgE elicits an immune response by binding to one of two Fc receptors. The high affinity receptor FcεRI is expressed only on mast cells and/or basophils. Aggregation of antigens and binding of IgE to the mast cell FcεRI results in degranulation and the release of mediators from the cells; binding to FcεRII on basophils causes release of type 2 cytokines (e.g., IL-4, IL-13) and other inflammatory mediators. The low affinity receptor FcεRII is constitutively expressed on B cells and inducibly expressed by IL-4 on macrophages, eosinophils, platelets and T cells.

Immunoglobulin G (IgG)

An immunoglobulin composed of two Fab and one Fc fragment. The Fabs include the antigen combining sites while the Fc region consists of the remaining constant sequence domains of the heavy chains and contains cell binding and complement binding sites. IgGs act on pathogens via agglutination, opsonization, activation of complement-mediated reactions against cellular pathogens and/or neutralization. Unlike other Igs, IgG can cross the placenta to the fetus as maternal antibodies. There are four known IgG subclasses. IgG2 differs from the rest in that it cannot be transferred across the placenta and IgG4 does not fix complement. IgG is present in serum at a concentration of 8-16 mg/ml.

Immunologic Memory

The capacity of an organism to mediate effective responses to previously encountered antigens. The majority of these responses are regulated by T cells.

In situ

A Latin phrase that literally means "in the place." It is used to refer to examination of a phenomenon in exactly the place where it occurs (e.g., organ perfusions). In oncology, in situ refers to malignant cells present as a tumor. They have not metastasized beyond the original site where the tumor was discovered.

In vitro

A Latin phrase that literally means "in glass." It is used to refer to a process or reaction (or experiment) occurring in an artificial environment (i.e., test tube, culture medium, etc.).

In vivo

A Latin phrase that literally means "in a living being." It is used to refer to a process or reaction (or experiment) occurring in a living body.

Indolent

Slowly progressing, low-grade; causing little or no pain.

Inflammation

The response of the immune system to an injury caused by irritation, infection, physical damage or chemically-induced cell stress. Local reactions at the site of injury cause immune cells to be recruited into the area, leading to the destruction and removal of the affected tissues and to wound repair. The five symptoms of inflammation are redness, heat, swelling, pain and dysfunction of the affected area, although not all five need be present at any one time.

Influenza

An acute viral respiratory tract infection caused by influenza viruses A, B or C. It is characterized by inflammation of the nasal mucosa, the pharynx and conjunctiva and by headache, generalized myalgia, fever and chills. Necrotizing bronchitis and interstitial pneumonia are seen with severe influenza and account for the susceptibility of patients to secondary bacterial pneumonia due to *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus*

aureus. The incubation period is one to three days and the disease can persist for three to ten days.

Influenza Pneumonia

Pneumonia caused by the damage done to the cells of the lung epithelium by the replication of influenza virus.

Influenza Virus

Serologically different viruses (A, B and C) from the orthomyxovirus family that cause influenza.

Inoculum

Cells or viruses added to start a culture or infect a culture of cells, respectively. It also refers to injection of biological material to induce immunity (i.e., a vaccine).

Interferon alfa (IFN-alpha)

A type I interferon mainly produced by leukocytes which shows predominantly nonspecific antiviral effects via interference with the synthesis of double-stranded RNA which is essential for the replication of some viruses. IFN-alpha is used in the treatment of hepatitis. This interferon is also overexpressed together with IFN-gamma in type 1 diabetes.

Interferon beta (IFN-beta)

Type I interferon mainly produced by fibroblasts, epithelial cells and macrophages. It shows predominantly nonspecific antiviral effects via interference with the synthesis of double-stranded RNA, which is essential for the replication of some viruses.

Interferon beta-1a (IFN beta-1a)

Glycosylated, recombinant mammalian-cell product, with an amino acid sequence identical to that of natural interferon beta. IFN-beta-1a is used in the treatment of multiple sclerosis.

Interferon beta-1b (IFN beta-1b)

Nonglycosylated recombinant bacterial-cell product in which serine is substituted for cysteine at position 17, with respect to natural interferon beta. IFN-1b is used in the treatment of multiple sclerosis.

Interferon gamma (IFN-gamma)

A type II interferon produced by T lymphocytes which shows marked immunoregulatory activity although its antiviral activity is less potent as compared to type I interferons. Overproduction of this inflammatory cytokine may be involved in autoimmune insulinitis, type 1 diabetes, IBD, rheumatoid arthritis and multiple sclerosis.

Interferon tau (IFN tau)

A recently discovered interferon that possesses activities similar to those observed for other type I interferons (IFN-alpha and IFN-beta), including antiviral, antiproliferative and immunomodulatory activities. IFN-tau has considerable potential for treatment of autoimmune and immunologically mediated disorders including multiple sclerosis and type 1 diabetes.

Interferons (IFNs)

Cytokines, small glycoproteins released from one or several cell types (i.e., leukocytes, fibroblasts and T lymphocytes) in response to antigen. Interferons have been classified into three main subtypes (alpha, beta and gamma) based on interaction with antibodies, chemical properties and cellular origin. Interferons are used in different pathologies.

Interleukin (IL)

A member of a class of cytokines (IL-1 through IL-29) produced by several cell types (i.e., lymphocytes, macrophages, monocytes, fibroblasts, astrocytes, endothelium, etc) with very diverse actions. Some of these actions include effects on stem cell division (IL-11); development and differentiation of B cells (IL-5) and Th1 cells (IL-12); T cell growth and activation (IL-2); lymphocyte growth (IL-6), etc.

Interleukin-1 (IL-1)

A soluble protein cytokine that is a member of the IL-1 superfamily which includes IL-1alpha, IL-1beta and the IL-1 receptor antagonist (IL-1RA). IL-1alpha and IL-1beta are proinflammatory cytokines that are involved in inflammatory and immune responses while IL-1RA competes for receptor binding with these two isotypes thus blocking inflammatory and/or immune activation. Both isotypes are secreted by monocytes, macrophages and/or accessory cells early during an immune response and they activate T and B cells, stimulate T cell proliferation and enhance T and B cell responses to antigens. Overproduction of IL-1 has been implicated in several diseases including COPD, rheumatoid arthritis, type 1 diabetes, Alzheimer's disease and inflammatory bowel disease (IBD) and inhibitors of this cytokine may be effective treatment options for these disorders.

Interleukin-1 Receptor (IL-1R)

The cytokine receptor that binds members of the IL-1 superfamily IL-1alpha, IL-1beta and IL-1 receptor, type I (IL-1RI/IL-1RA). There are two identified subtypes: type I (CD121a) and type II (CD121b) which are involved in cytokine-induced immune and inflammatory responses. Antagonism of these receptor subtypes may be effective in the treatment of inflammatory diseases such as COPD.

Interleukin-10 (IL-10)

A cytokine released by Th2 cells that can inhibit cytokine release from Th1 cells. In addition, during late-phase inflammatory reactions, IL-10 upregulates expression of cellular adhesion molecules on endothelial and epithelial cells that are involved in recruitment of inflammatory cells from the circulation. IL-10 has been implicated in the pathogenesis of systemic lupus erythematosus. It inhibits the synthesis and release of proinflammatory cytokines produced by stimulated monocytes and macrophages and is under development for rheumatoid arthritis. Psoriatic lesions show significantly low levels of IL-10 and studies suggest that this cytokine may be an effective treatment for psoriasis.

Interleukin-11 (IL-11)

A pleiotropic antiinflammatory cytokine that modulates antigen-specific antibody responses, potentiates megakaryocytes and regulates bone marrow adipogenesis. IL-11 has been shown to act synergistically with IL-10 to inhibit proinflammatory cytokine production and it decreases TNF-alpha, IL-1 and IL-12 production due to inhibition of NFkappaB. IL-11 may be effective as a treatment for psoriasis.

Interleukin-12 (IL-12)

A heterodimeric cytokine that promotes cell-mediated immunity by facilitating type 1 helper T lymphocyte responses, including the production of IFN-gamma by both T cells and natural killer cells, potentiating the lytic activity of natural killer cells and boosting specific cytolytic T lymphocyte responses. IL-12 has shown potent therapeutic effects in various cancers and infectious diseases, including some viral infections. Overproduction of this inflammatory cytokine may be involved in autoimmune insulinitis, type 1 diabetes, IBD, rheumatoid arthritis, psoriasis and multiple sclerosis.

Interleukin-13 (IL-13)

Immune regulatory cytokine, predominantly produced by activated Th2 cells and mast cells, that inhibits the production of inflammatory cytokines in monocytes. IL-13 upregulates expression of cellular adhesion molecules on endothelial and epithelial cells during late-phase inflammatory reactions. Following an early-phase allergic reaction in which allergen crosslinking of IgE bound to mast cells occurs, IL-13 (in addition to IL-4, IL-5 and GM-CSF) selectively recruits and activates eosinophils, other Th2 lymphocytes and IgE-secreting B lymphocytes into airway mucosa.

Interleukin-15 (IL-15)

A cytokine expressed by monocytes, macrophages, dendritic cells (DC), keratinocytes, fibroblasts and nerve cells. It binds to and signals through a complex composed of the IL-2/IL-15

receptor beta chain (CD122) and the common gamma chain (gamma-C, CD132). It is expressed by T cells, monocytes and keratinocytes in psoriatic epidermis that affects T, B and NK cell division, neutrophil and monocyte activation. It also inhibits lymphocyte apoptosis. Keratinocyte-derived IL-15 has been shown to inhibit keratinocyte and lymphocyte apoptosis and it may play a role in the survival of infiltrating lymphocytes and abnormal keratinocytes features in psoriasis. This cytokine has been implicated as playing a role in rheumatoid arthritis and is overexpressed in psoriasis and pulmonary inflammatory diseases. IL-15 accumulates within synovial lesions and induces the overproduction of IL-17 within rheumatic joints. In addition, IL-15 neutralization has been shown to be beneficial in preclinical models of psoriasis, diabetes and celiac disease. IL-15 is normally not secreted. However, viral infection can cause its secretion.

Interleukin-17 (IL-17)

IL-17 is a family of cytokines whose members include IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25) and IL-17F. These cytokines are associated with many immune regulatory effects and are associated with mediation of proinflammatory and allergic responses. IL-17 induces cytokine (e.g., IL-6, G-CSF, GM-CSF, IL-1beta, TGF-beta, TNF-alpha), chemokine (e.g., IL-8, GRO-alpha and MCP-1) and prostaglandin (e.g. PGE2) production from several cell types (e.g., fibroblasts, endothelial cells, epithelial cells, keratinocytes, monocytes and macrophages). IL-17 is secreted by the novel T helper cell subset Th17 which induces autoimmune inflammation and IL-17 receptor signaling may play a role in the development of chronic destructive arthritis from acute synovitis; IL-17 contributes both directly and indirectly to the bone and cartilage destruction occurring in rheumatoid arthritis. IL-17 may also be involved in the stimulation of osteoclastogenesis. The IL-17 family has been linked to other immune/autoimmune related diseases including asthma (i.e., plays a role in airway remodeling), lupus, allograft rejection, ankylosing spondylitis and antitumor immunity.

Interleukin-18 (IL-18)

A proinflammatory cytokine structurally and functionally related to the IL-1 family of proteins that is a strong inducer of IFN-gamma production by T lymphocytes and NK cells. It is the only cytokine that can induce T helper 1 (Th1) and T helper 2 (Th2) cell polarization depending on immunologic context. It is implicated in several immune-mediated diseases. It is involved in both innate and acquired immunity and its inflammation-promoting role is IFN-gamma-independent. It also plays a role in the local inflammation seen in rheumatoid arthritis. It is currently under investigation as an immunotherapeutic cancer agent and as an angiogenic factor.

Interleukin-18 Binding Protein (IL-18BP)

A constitutively secreted glycoprotein protein that exerts antiinflammatory and immunosuppressive effects. By preventing interleukin 18 (IL-18) receptor binding, it inhibits IL-18 and interferon (IFN)gamma production. Four human splice variants have been identified (IL-18BP_a, IL-18BP_b, IL-18BP_c, IL-18BP_d) of which IL-18BP_a is the predominant form exhibiting the highest affinity for IL-18. While IL-18BP_c also neutralizes IL-18, IL-18BP_b and IL-18BP_d cannot bind to or neutralize cytokine. Inhibition of IL-18BP would be effective in suppressing high circulating levels IL-18 observed in many autoimmune diseases such as psoriasis, rheumatoid arthritis, inflammatory bowel disease psoriatic arthritis and in sepsis.

Interleukin-1beta (IL-1beta)

A cytokine released by mast cells following allergen-IgE binding that upregulates expression of cellular adhesion molecules on endothelial and epithelial cells during late-phase inflammatory reactions. It is also released by epithelial cells and astrocytes. An upregulation of IL-1beta production by the microvasculature has been observed in Alzheimer's disease and in response to ischemic insult. See also Interleukin-1 (IL-1)

Interleukin-2 (IL-2)

IL-2 is a cytokine produced by CD4⁺ T lymphocytes upon activation by antigens and costimulators. It promotes T cell clonal expansion in the adaptive immune response and can activate B lymphocytes, monocytes and NK cells. Binding of IL2 to its receptor activates the JAK/STAT, PI3-kinase and RAS signaling pathways. Alpha chain monomers (CD25) conform a

low affinity IL2 receptor. High affinity and intermediate affinity IL2 receptors are conformed by alpha/beta heterodimers and beta chain monomers, respectively, associated to a gamma chain. It plays a role in both proliferative and activation-induced cell death (AICD) signaling of T cells. MS is in part genetically determined and the gene encoding the alpha-chain of the IL-2 receptor, IL2RA, harbors alleles associated with risk to MS and other autoimmune diseases such as GVHD. In addition, IL2RA genetic variants correlate with the levels of a soluble form of the IL-2 receptor in subjects with type 1 diabetes and multiple sclerosis (MS). IL-2 is produced by activated T cells in the synovium during the early stages of rheumatoid arthritis and in psoriatic lesions.

Interleukin-20 (IL-20)

A new member of the IL-10 family (including IL-19, IL-22, IL-24 and IL-26) of cytokines which signals through the IL-20R1/IL-20R2 heterodimer. Together with IL-19, it is synthesized by a distinct population of keratinocytes. IL-20 induces keratin proliferation and Stat-3 signal transduction pathway and may be implicated in the pathogenesis of psoriasis.

Interleukin-23 (IL-23)

A heterodimeric cytokine composed of a unique p19 subunit and the p40 subunit component of IL-12. It is secreted by activated dendritic cells (DCs) and macrophages and binds to memory T cells, NK cells, macrophages and DCs. In particular, this cytokine is suspected to be involved in the activation and maintenance of the Th17 subset of inflammatory T cells. It has been hypothesized that the autoimmune actions of IL-12 are attributable to IL-23 since mice lacking IL-23p19 (only IL-23 absent) and mice lacking IL-12p40 (both IL-12 and IL-23 absent) were protected from autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA). On the other hand, mice lacking IL-12p35 (only IL-12 absent) developed more severe disease. Overexpression of IL-23 and/or IL-12 or defect in their receptors may be involved in conditions such as rheumatoid arthritis, psoriatic arthritis, psoriasis, multiple sclerosis, Crohn's disease and ankylosing spondylitis. Patients with Crohn's disease have been shown to have a significantly increased number of intestinal CD14⁺ macrophages as compared with normal control subjects and these cells produce larger amounts of IL-23 and TNF-alpha as compared to normal controls or patients with ulcerative colitis. Moreover, genomic studies conducted in patients with Crohn's disease have identified the IL-23 pathway as playing a predominant role in this disorder. Monoclonal antibodies directed against both IL-12 and IL-23 may be effective treatment options for these diseases.

Interleukin-3 (IL-3)

A multilineage cell growth inducing cytokine (hemopoietic colony stimulating factor) secreted by lymphocytes, epithelial cells and astrocytes which stimulates clonal proliferation and differentiation of various types of blood and tissue cells.

Interleukin-4 (IL-4)

Pleiotropic, immune regulatory cytokine released by Th2 and mast cells that upregulates expression of cellular adhesion molecules on endothelial and epithelial cells during late-phase inflammatory reactions. Following an early-phase allergic reaction in which allergen crosslinking of IgE bound to mast cells occurs, IL-4 (in addition to IL-5, IL-13 and GM-CSF) secreted by Th2 cells selectively recruits and activates eosinophils, other Th2 lymphocytes and IgE-secreting B lymphocytes into airway mucosa. Eosinophil infiltration of airway submucosa and mucosa is characteristic allergic diseases. Like IL-12, this cytokine has been found to inhibit HIV-1 replication in primary blood-derived human macrophages. Antagonizing the effects of IL-4 is a potential new approach for the treatment of for asthma, allergic rhinitis and rheumatoid arthritis. IL-4 receptors are overabundant in several tumor types therefore IL-4 fusion toxins may be an effective treatment for some forms of cancer (i.e., breast cancer).

Interleukin-5 (IL-5)

A proinflammatory cytokine released by Th2 and mast cells that is involved in the development and differentiation of eosinophils and B cells; it also upregulates expression of cellular adhesion molecules on endothelial and epithelial cells during late-phase inflammatory reactions. Following an early-phase allergic reaction in which allergen crosslinking of IgE bound to mast cells occurs, IL-5 (in addition to IL-4, IL-13 and GM-CSF) secreted by Th2 cells selectively recruits

and activates eosinophils, other Th2 lymphocytes and IgE-secreting B lymphocytes into airway mucosa. IL-5 is essential for eosinophilic inflammation which leads to airway hyperresponsiveness. Antagonizing the effects of IL-5 or inhibiting its production are potential new approaches for the treatment of allergic disease such as asthma and allergic rhinitis.

Interleukin-6 (IL-6)

A member of a subfamily of related hematopoietic, proinflammatory cytokines, including leukemia inhibitory factor, ciliary neurotrophic factor, oncostatin M, cardiotrophin-1 and IL-11. The expression of IL-6 in the brain has been found to be increased in neurological disorders such as Alzheimer's disease, Parkinson's disease, trauma, stroke and meningitis. IL-6 is also present in abnormally high levels in obesity and type 2 diabetes, and has been implicated in inflammatory bowel disease. IL-6 is upregulated in epithelial cells infected with rhinoviruses and overexpression of IL-6 have been observed in the synovium in the early stages of rheumatoid arthritis, at systemic and cutaneous levels in psoriasis and in human systemic lupus erythematosus. IL-6 in the presence of sex steroids is required for osteoclastogenesis to occur.

Interleukin-8 (IL-8)

An ELR+ (Glu-Leu-Arg) CXC chemokine suggested to be an important mediator of angiogenesis that may contribute to plaque formation in human coronary atherosclerosis. Overproduction of IL-8 may also be involved in airway inflammation characteristic of cystic fibrosis, asthma, the common cold and rheumatoid arthritis; IL-8 may also play a role in the inflammatory processes involved in psoriasis. Ischemia has been shown to increase the production of IL-8 in the brain. see Also Interleukin 8 beta Receptor (IL-8betaR)

Interleukin-8 (IL-8) beta Receptor

One of two G-protein-coupled receptor subtypes (alpha and beta) for interleukin 8 (IL-8), an ELR+ (Glu-Leu-Arg) CXC chemokine (chemokine CXCR2) produced by monocytes, fibroblasts and endothelial cells that mediates activation and chemotaxis of T cells, monocytes and neutrophils. Overexpression of IL-8 appears to be involved in airway inflammation characteristic of COPD as well as cystic fibrosis, asthma, the common cold and rheumatoid arthritis. Antagonism of this receptor could prevent recruitment of pathogenic cells into inflamed lungs thus preventing development of COPD. Antagonism of this receptor may also be effective in the treatment of psoriasis and atherosclerosis since IL-8 may also play a role in the inflammatory processes involved in psoriasis and angiogenesis that may contribute to plaque formation in human coronary atherosclerosis. Ischemia has also been shown to increase the production of IL-8 in the brain.

Interleukin-9 (IL-9)

A cytokine secreted from CD4+ T cells that affects T cell and mast cell division/development. It may also be involved in the pathogenesis of asthma by enhancing the effects of other cytokines and inflammatory mediators. The normal nonasthmatic state is suggested to be associated with downregulation of IL-9.

iRNA

See RNA Interference (RNAi)

J

K

Knockin

A genetically modified mutant organism (e.g., mouse, yeast) that carries a particular gene that is not normally present. The effect of including this gene can be provide information about a specific disease or condition.

Knockout

Experimental inactivation of specific genes in laboratory organisms (e.g., mice, yeast) in order to study a specific disease or condition.

Koch's Postulates

The classical requirements for disease causation that were developed by Henle and Koch in the 19th century. They are i) the infectious microorganism is present in all individuals suffering from the disease; ii) the microorganism can be isolated from the diseased host and grown in pure culture on artificial laboratory media; iii) inoculation of a healthy susceptible laboratory animal with the freshly isolated microorganism results in induction of the disease that was seen in the original host animal; and, iv) the microorganism can be reisolated in pure culture from an experimentally infected host.

L

Legionella

A genus of rod- or coccus-shaped aerobic Gram-negative bacteria. Certain species such as *L. pneumophila*, produce Legionnaires' disease, a severe form of pneumonia.

Leukocyte

A member of a heterogeneous cell population, also known as white blood cells, found in various tissues and circulating blood that is formed in myelopoietic, lymphoid and reticular portions of the reticuloendothelial system. These cells represent three lines of development according to primitive origin, which includes myeloid (generating neutrophil, basophil and eosinophil granulocytes), lymphoid (generating B and T cells) and monocytic (generating monocytes and macrophages).

Leukopenia

An abnormal decrease in the number of white blood cells.

Lymphocyte

A type of white blood cell formed in lymphocytic tissue (i.e., lymph nodes, spleen, thymus, tonsils, Peyer's patches, bone marrow) that is responsible for specific immune recognition of pathogens and the initiation of adaptive immune responses.

Lymphocytosis

An increased number of circulating lymphocytes. Pathologic lymphocytosis occurs in chronic inflammation, recovery from acute infection, lymphocytic leukemia and hypoadrenocorticism and indicates a strong immune stimulus of chronic duration from a bacterial infection, viremia or immune-mediated disease. Absolute lymphocytosis is the presence of more than 15,000 lymphocytes/mm³ blood.

M

Macrophage

An immune cell that is capable of phagocytosis, and that may also be capable of antigen processing and presentation (APCs). These cells have different names depending upon the tissue in which they are located (e.g., Kupffer cells in the liver, alveolar macrophages in lung, histiocytes in connective tissue). Macrophages process the phagocytosed antigen and present it in association with class II molecules to CD4⁺ T cells. If the CD4⁺ T cell is Th0, antigen presentation by macrophages often results in differentiation of these Th0 cells into Th1 cells. Phagocytosis and/or cytokines induce macrophage activation, and activated macrophages secrete IL-1 and upregulate expression of costimulatory molecules (e.g., B7 and ICAM-1) on their surface.

Major Histocompatibility Complex (MHC)

The genetic loci (class I, II and III regions) found in all mammals encoding a specialized group of highly polymorphic cell surface proteins responsible for antigen recognition. Class I and II MHC gene products are involved in signaling between lymphocytes and cells expressing antigen.

Class III molecules are structurally and functionally different from the gene products of class I and II MHC and are commonly referred to as the complement system.

MAP Kinase

See Mitogen Activated Protein (MAP) Kinase (MAPK)

MAPK

See Mitogen Activated Protein (MAP) Kinase (MAPK)

Matrix Metalloproteinases (MMPs)

A family of zinc-dependent enzymes also known as matrixins that catalyze the hydrolysis of peptide chains and therefore have the ability to degrade a variety of proteins (i.e., elastin, collagen, proteoglycans, laminin, fibronectin) of the extracellular matrix. They are functionally categorized into three groups according to their substrate target: collagenases, stromelysins and gelatinases which degrade fibrillar collagen, proteoglycans and glycoproteins and denatured and basement membrane collagens, respectively. MMPs are produced by neutrophils, alveolar macrophages and airway epithelial cells and have been implicated in several clinical inflammatory conditions such as COPD and asthma where inhibition would block extravasation, migration and alveolar wall degradation. Inhibitors may also be effective as a treatment for rheumatoid arthritis, inflammatory bowel disease (IBD), stroke and multiple sclerosis and for preventing tumor growth and metastasis.

MEK

See Mitogen-Activated Protein (MAP) Kinase Kinase (MEK; MAP2K)

Metaplasia

The reversible replacement of one differentiated cell type with another mature differentiated cell type. This results in transformation of one tissue type to another.

Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

The coronavirus that causes the viral respiratory illness, MERS (Middle East respiratory syndrome). MERS-CoV is a species in lineage C of the genus beta coronavirus. It is different from the coronavirus that causes severe acute respiratory virus (SARS) and appears to most closely resemble the not-yet-classified viruses from insectivorous European and African bats in the Vespertilionidae and Nycteridae families. Infection by this virus appears to be primarily zoonotic in nature, with limited human-to-human transmission. Symptoms of infection include flu-like illness with signs and symptoms of pneumonia (e.g., fever, cough, shortness of breath, nausea, vomiting, diarrhea). Symptoms are similar to those found in SARS infections with the exception that renal failure has only been reported in MERS-CoV infection.

Missense Mutation

A mutation that converts a codon coding for one amino acid to a codon coding for another amino acid.

Mitochondria

A class of tubular-shaped organelles that reside within eukaryotic cells, converting oxygen and nutrients into adenosine triphosphate (ATP), which is required by cells for energy. Mitochondrial dysfunction has been hypothesized to contribute to the pathogenesis of Huntington's disease, Parkinson's disease, schizophrenia, and a wide range of other disorders.

Mitogen-Activated Protein (MAP) Kinase (MAPK)

A family of serine/threonine kinases that are activated when quiescent cells are exposed to mitogens and therefore potentially transmit a signal for entry into the cell cycle. One target is transcription factor p62TCF. MAPK can be phosphorylated by MAP kinase kinase (MAPKK) which is controlled by RAF1. C-Jun N-terminal kinases (JNK) are members of the MAPK family of enzymes. MAPK has been implicated in cerebral spasm and inhibitors of this kinase may be useful in the treatment of vasospasm following subarachnoid hemorrhage. See also p38 Mitogen-Activated Protein Kinases (MAPKs)

Mitogen-Activated Protein (MAP) Kinase Kinase (MEK; MAP2K)

A kinase enzyme (EC 2.7.12.2) and member of MAPK signal transduction cascade where it lies upstream of MAPK and stimulates the enzymatic activity of MAPK. MAPKs, also known as extracellular signal-regulated kinases (ERKs), are activated by a wide variety of extracellular signals and thus serve as an integration point for multiple biochemical pathways. They are activated via rapid phosphorylation on threonine and tyrosine residues. The MAPK signaling cascade is initiated by extracellular signaling which activates (i.e., phosphorylates) MAP kinase kinase kinase (MKKK; MAP3K). Activated MAP3K phosphorylates MEK which then activates MAPK. MEK/ERK inhibitors inhibit mucin secretion which would be potentially effective as a treatment for the airway mucus hypersecretion seen in COPD and other respiratory disorders such as asthma and cystic fibrosis. MEK inhibitors have also been shown to inhibit muscarinic receptor-induced human lung fibroblast proliferation which contributes to the pathology of COPD. In Crohn's disease, macroscopically noninflamed colon contributes to diarrhea via impaired epithelial sodium channel-mediated sodium absorption and studies have shown that therapeutic inhibition of MEK1/2 restores electrogenic sodium absorption. Thus, inhibition of MEK could be an effective strategy for the treatment of the chronic inflammation and diarrhea seen in Crohn's disease.

MMP

See Matrix Metalloproteinases (MMPs)

Monoclonal Antibody (MAb)

An antibody of a defined specificity that recognizes only a single epitope of an antigen. MAbs are produced by a single clone of B lymphocytes. Production of MAbs for therapeutic use is usually carried out by fusion of the relevant B cell clone with an immortalized cell line. This results in a population of hybrid cells (i.e., hybridoma) that secretes a large amount of the MAb of interest. Therapeutic MAbs can be murine, chimeric or humanized. Murine MAbs are developed in mice and can result in marked human antimouse responses (i.e., immunogenicity) in humans following administration. Thus, chimeric antibodies were developed which are composed of the murine variable region grafted onto a human MAb (two-thirds human). Humanized MAbs are less immunogenic since only the complementary determining regions of the murine antibody (only 5%) are grafted onto a human MAb.

Mutation

Damage or change in a gene or chromosome so that transcription is altered.

Myalgia

Pain in a muscle or muscles.

Mycoplasma

Prokaryotic microorganisms lacking cell walls and therefore resistant to many antibiotics. An example is *Mycoplasma pneumoniae* is responsible for pneumonia in humans and some domestic animals.

N**Nausea**

The unpleasant sensation of queasiness or stomach upset that often precedes or accompanies the act of vomiting. Some common causes include motion, early pregnancy, intense pain, emotional stress, gallbladder disease, food poisoning, enteroviruses among others. It is also an adverse effect of several chemotherapeutic agents.

Necrosis

Death of one or more cells of a tissue or organ. Early damage includes irreversible mitochondrial (e.g., swelling, granular calcium deposits) and nuclear (e.g., pyknosis, karyolysis, karyorrhexis) changes. Later, affected cells merge forming a focus of granular, amorphous or hyaline material.

Neuron

The cell of the nervous system which is composed of a cell body, dendrites and a single axon.

Neutrophil

See Polymorphonuclear Leukocytes.

Nosocomial

A disease acquired or occurring in a hospital.

Nucleocapsid (NC)

The coat (capsid) of a virus plus the enclosed nucleic acid genome.

Nucleoside

The building block of DNA and RNA which is a purine or pyrimidine base linked glycosidically to ribose or deoxyribose. It lacks the phosphate residues that would make it a nucleotide. The ribonucleosides are adenosine, guanosine, cytidine and uridine and the deoxyribosides are deoxyadenosine, deoxyguanosine, deoxycytidine and deoxythymidine.

Nucleotide

The phosphate ester of a nucleoside that is the basic constituent of DNA and RNA. Other structures (e.g., cAMP, cGMP) and molecules with two or three phosphates are also called nucleotides.

O

Open Reading Frame (ORF)

Part of a reading frame that has the potential to code for a protein or peptide. An ORF is a continuous stretch of codons that do not contain a stop codon (usually UAA, UAG or UGA).

Open-Label Trial

A clinical study in which all participants (i.e., patient and investigator) know the identity of the administered drug.

Orphan Drug

A status granted by the FDA to unpatentable medications developed for rare diseases. Rare or orphan diseases are defined affecting fewer than 200,000 people in the US or are associated with a low prevalence of less than 5 per 10,000 in the community. This status gives the manufacturer a seven-year right to exclusively market the compound. By increasing profitability of these agents, their production is encouraged.

Orthomyxoviridae

A family comprised of the influenza and togotoviruses that are characterized by negative sense, single-stranded, segmented RNA genomes.

P

p38 MAP Kinase

See p38 Mitogen-Activated Protein Kinases (MAPK)

p38 Mitogen-Activated Protein Kinases (MAPKs)

A class of MAPKs composed of four isoforms: p38 MAPK-alpha (MAPK14), p38 MAPK-beta (MAPK11), p38 MAPK-gamma (MAPK12) and p38 MAPK-delta (MAPK13 or SAPK4) which are activated by a variety of cellular stresses including osmotic shock, inflammatory cytokines, lipopolysaccharides (LPS), ultraviolet light and growth factors. They are activated via MAP3K and MEK by phosphorylation at Thr180 and Tyr182. Activated p38 MAPKs have been shown to phosphorylate and activate mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2) and the transcription factors ATF-2, Mac and MEF2. p38 MAPKs may also be involved in mucin secretion and inhibitors of this kinase could be potentially effective as a treatment for the airway mucus hypersecretion seen in COPD and other respiratory disorders and may also inhibit lung fibroblast proliferation which contributes to the pathology of COPD.

Palliative

A treatment directed toward the control of symptoms rather than the curing of the disease.

Pandemic

A global epidemic of an especially strong and highly infectious virus, newly infectious for humans, with the potential to cause many cases of illness and death due to a lack of acquired immunity in the human population.

Pangolin

A mammal that is also known as the scaly anteater.

Paramyxoviridae

A family of Class V enveloped RNA viruses. Its genome consists of a single negative strand of RNA and it has a helical nucleocapsid associated with virus-specific RNA polymerase (transcriptase). Other related viruses include Newcastle disease virus, measles virus and the parainfluenza viruses. Paramyxovirus is a genus of this family of which human parainfluenza virus type 1 is a member. Virions have both hemagglutinin and neuraminidase activity and encode a C protein.

PCR

See Polymerase Chain Reaction (PCR)

Peplomer

A part or subunit of the peplos of a virion. See Also Peplos

Peplos

The coat or envelope of lipoprotein material that surrounds certain virions.

Peripheral Blood Mononuclear Cells (PBMCs)

Lymphocytes and monocytes isolated from peripheral blood by centrifugation.

Phase 0 Trial

A phase of clinical testing that is also known as exploratory IND in the US and Microdosing in Europe. This stage of drug development is intended to facilitate the transition from animal to human studies. The trials evaluate doses determined in animal studies that are only 1/100th of those expected to be required for therapeutic effect.

Phase I Trial

The first human study of a new drug, usually conducted in a small number of healthy individuals to evaluate the biological properties of that drug, including pharmacological activity, pharmacokinetics and tolerability (i.e., toxicity). Examination of how the drug should be administered, how often and in what dosage are also assessed.

Phase II Trial

A type of study providing preliminary information on the efficacy and safety of a new drug. Phase IIa trials are conducted in a small population of patients, while phase IIb studies incorporate larger patient cohorts and can determine a range of doses to be used in phase III clinical trials.

Phase III Trial

A full-scale clinical study conducted in order to determine the efficacy and safety of a new drug prior to seeking marketing approval. These studies usually involve large patient populations randomized to receive a new or standard therapy and/or placebo.

Phase IV Trial

A large-scale clinical trial conducted following regulatory approval of a drug. Its purpose is to expand efficacy and safety information. These trials are also referred to as marketing support trials.

Phenotype

The observable traits of an organism (e.g., weight, height, hair color) regardless of the genotype. Phenotypic traits are not necessarily genetic and may result from an interaction between the genotype and the environment.

Placebo

An inactive compound used in preclinical and clinical trials as a comparison for active compounds.

Pleiotropic

Having multiple effects.

Pneumocystis carinii

A protozoon microorganism (e.g., frequently a eukaryotic yeast) that is now classified as *Pneumocystis jirovecii*. See *Pneumocystis jirovecii*

***Pneumocystis carinii* Pneumonia (PCP)**

See *Pneumocystis jirovecii* Pneumonia (PJP)

Pneumocystis jirovecii

A protozoon microorganism (e.g., frequently a eukaryotic yeast) that was previously classified as *Pneumocystis carinii*. It is responsible for pneumocystis pneumonia in immunocompromised individuals.

***Pneumocystis jirovecii* Pneumonia (PJP)**

A serious illness caused by the fungus *Pneumocystis jirovecii*. PJP is an interstitial pneumonia and one of the most frequent and severe opportunistic infections in people with weakened immune systems, particularly people with HIV/AIDS. It also occurs in individuals treated with steroids, the elderly or premature or debilitated babies. Formerly known as *Pneumocystis carinii* pneumonia (PCP).

Pneumonia

Inflammation of the lungs with consolidation. Pneumonia is a form of acute respiratory infection that inflames the alveoli in the lungs which in healthy individuals fill with air during inhalation. When infected, these air sacs may fill with fluid or pus, leading to symptoms such as cough with phlegm, fever, chills, chest pain and difficulty breathing. Pneumonia may be caused by a variety of organisms, including bacteria, viruses and fungi. Pneumonia can be classified into community-acquired pneumonia, hospital-acquired pneumonia, pneumonia in the immunocompromised and aspiration pneumonia (i.e., caused by inhaled food, drink, vomit or saliva from the mouth into the lungs and can lead to pus formation in the lung cavity). See also Consolidation

Polymerase

A general term for any enzyme belonging to the EC class 2, transferases which catalyze polymerization. Prokaryotic DNA polymerases are divided into types I, II and III, while eukaryotic polymerase is subdivided into polymerase alpha, -beta, -gamma, -delta and -epsilon. DNA polymerases are highly accurate, entering the correct complementary base opposite a base on the template chain; there is a low incidence of mismatching. DNA polymerases remove primers after they have served their function, refilling the gaps with nucleotides until all bases are paired. However, DNA polymerase cannot link the last nucleotide added to the 5' end of the next-to-the-last segment; a single-chain nick remains that is later closed by DNA ligase. RNA polymerase catalyzes RNA transcription (a polymerization reaction). There are three types of eukaryotic RNA polymerase and only one bacterial RNA polymerase.

Polymerase Chain Reaction (PCR)

A technique developed in 1983 by K.B. Mullis and F. Faloona which simplifies the production of multiple DNA copies from a sample taking advantage of DNA polymerase, the enzyme which

catalyzes DNA replication. During the first cycle of PCR, a DNA double helix containing the nucleotide sequence of interest is unwound by heating to 90°C. DNA polymerase and the nucleotide triphosphates (adenine, thymine, cytosine and guanine) required for replication are added to the unwound DNA mixture. Artificially synthesized, short (about 20 to 30 nucleosides in length) DNA, complementary to the ends of the unwound template chains, are also added and serve as the primers for the reaction. The mixture is cooled to 60°C, allowing the artificial primers to wind to the ends of the template chains. Replication then occurs where DNA polymerase assembles complementary copies of the template chains starting from the artificial primers. The resulting reaction mixture now contains twice as many DNA molecules. The second cycle is initiated by heating the reaction mixture again which results in unwinding of the newly synthesized double helices. The mixture is then cooled allowing additional copies of the artificial primer chains to rewind with the ends of the template chains (as in the first cycle). DNA polymerase makes copies of the artificial chains and at the end of this cycle, the number of DNA molecules has doubled again. Each time the heating and cooling cycle is repeated, the number of DNA molecules in the sample doubles and, since cycling time is short, hundreds of billions of DNA copies can be generated in a few hours.

Polymerization

The linkage of glucose units into chains in cellulose or starch molecules. Multiple identical or nearly identical subunits called monomers are linked together in a chain to form a polymer. This process underlies the assembly of most biological macromolecules. For example, monosaccharides polymerize into polysaccharides, amino acid monomers into proteins and nucleotide monomers into nucleic acid polymers.

Polymorphonuclear Leukocytes

White blood cells with multilobed nuclei and cytoplasmic granules. They include neutrophils (granules stain with neutral dyes), eosinophils (granules stain with eosin) and basophils (granules stain with basic dyes).

Preclinical Studies

Experimental in vitro and/or in vivo testing in animals performed prior to clinical studies to determine the biological activity and safety of an agent.

Prevalence

The number of cases of a disease or condition at a given time.

Prognosis

An assessment of the likely outcome of the disease judged from general experience of the disease and the age and condition of the individual patient.

Programmed Cell Death (PCD)

See Apoptosis

Proliferation

Growth and reproduction of similar cells.

Prophylaxis

The prevention of a disease or the process leading to a disease.

Prophylaxis, Active

Administration of an antigenic agent to actively stimulate an immune mechanism.

Prophylaxis, Passive

Use of antiserum from another individual or animal to provide temporary (7-10 days) protection against a specific infectious or toxic agent.

Protease

Proteolytic enzymes including both endopeptidases (EC 3.4.21-24 & 3.4.99) and exopeptidases (EC 3.4.11-19), which hydrolyze peptide bonds leading to degradation of a protein (i.e., proteolysis). Proteases are classified into four general types: serine, cysteine, aspartic and matrix metalloproteinases (MMPs).

Proteasomes

Proteolytic complexes that degrade the majority of short-lived cytosolic and nuclear proteins. They are implicated in ATP-dependent ubiquitin protein complex degradation and in antigen processing in antigen presenting cells. Proteasomes are also involved in the regulation of JAK/STAT pathways, IL-2, IL-3 and erythropoietin stimulation. Proteasome inhibitors down-regulate inflammatory mediators such as NFkappaB and may be a potential treatment for stroke and myocardial infarction. Proteasome inhibitors also induce apoptotic cell death, and thus are being studied for the treatment of cancer.

Proteolysis

The degradation of proteins via hydrolysis of the peptide bonds resulting in the formation of smaller polypeptides. The process is catalyzed by proteolytic enzymes (e.g., protease, peptidase), acids or bases. See also Protease

Q

R

Recombinant

Describes a cell or an individual with a new combination of genes not found together in either parent; it usually refers to linked genes. Recombinant DNA is spliced DNA formed from 2 or more different sources that have been cleaved by restriction enzymes and joined by ligases.

Recombinant Vaccine

Use of a recombinant antigen preparation in combination with an adjuvant, which may be administered prophylactically or therapeutically to induce viral neutralizing proteins and other protective immune responses.

Refractory

A disease or infection that is resistant to treatment.

Renin

An enzyme (EC 3.4.23.15) that catalyzes the cleavage of the leucine-leucine bond in angiotensinogen to generate angiotensin I. It is synthesized as an inactive protein in the kidney and released into the blood in the active form in response to various metabolic stimuli.

Renin-Angiotensin System

A system consisting of renin, angiotensin-converting enzyme (ACE) and angiotensin II that regulates blood pressure and electrolyte and fluid balance. Renin, an enzyme produced in the kidney, acts on angiotensinogen, an alpha-2 globulin produced by the liver, resulting in formation of inactive angiotensin I. ACE in the lung acts on angiotensin I in the plasma converting it to angiotensin II.

Angiotensin II is a potent pressor substance that causes contraction of the arteriolar smooth muscle, aldosterone release and renal absorption of sodium; it also has other indirect actions mediated by the adrenal cortex. This system is a target for the treatment of arterial hypertension.

Replicon

A tandem region of replication (about 30 microns in length) in a chromosome derived from an origin of replication (i.e., a regions of DNA required for initiation of replication) that must also contain an origin of replication.

Respiratory Syncytial Virus (RSV)

A RNA virus that is a major pathogen causing upper and lower respiratory tract infections in infants and younger children. Infection manifests as bronchiolitis, pneumonia and croup. It is an RNA virus that is a member of the Paramyxoviridae family.

Retrovirus

A virus that contains RNA as its genetic material. This RNA is translated into DNA which inserts into the DNA of a viral-infected cell. Retroviruses are responsible for many diseases including some cancers and AIDS.

Rhinitis

An inflammation of the nasal passage which is characterized by frequent and/or repetitive sneezing, runny or congested nose and itchiness of the nose, eyes and throat and may also be associated with headache, impaired smell, postnasal drip, conjunctival symptoms and sinusitis. The most common form of rhinitis is allergic rhinitis which is classified as perennial, seasonal or occupational, depending on the time of allergen exposure. Less common subtypes include hormonal rhinitis (occurring during pregnancy or in patients with hypothyroidism), nonallergic or vasomotor rhinitis, infectious rhinitis and drug-induced rhinitis.

Rhinorrhea

A runny nose. See also Coryza

Rhinovirus

A member of the Picornaviridae family of viruses that commonly infects the upper respiratory tract. These viruses are responsible for the common cold virus and foot-and-mouth disease. Human rhinoviruses (HRV) are grouped according to receptor tropism, sensitivity to antiviral agents, antigenicity or genetic similarity. There are 102 different HRV serotypes. The major genetic clade for HRV species is HRV-1 (91 serotypes) that uses ICAM-1 as a receptor; HRV-1A (76 serotypes) and HRV-1B (25 serotypes) are antigenic subtypes of this group. HRV-2 (10 serotypes) that uses the LDL receptor. See also Picornaviridae

Ribonucleases (RNAases)

A family of nucleases (EC 2.7 and EC 3.1) that catalyze the hydrolysis of internucleotide phosphodiester bonds in RNA into smaller components thus degrading it. They can be divided into endoribonucleases and exoribonucleases which include further sub-classes (i.e., EC 2.7 phosphorolytic enzymes and EC 3.1 hydrolytic enzymes).

Ribonucleic Acid (RNA)

A macromolecule consisting of ribonucleoside residues connected by phosphate from the 3'-hydroxyl of one to the 5'-hydroxyl group of the next nucleotide. It is found in all cells in both the nuclei and cytoplasm and in viruses. RNA is divided into fractions depending on location, form or function. Messenger RNA (mRNA) reflects the exact nucleoside sequence of genetically active DNA. mRNA carries the message of the DNA coded within its sequence to the cytoplasmic areas where protein is assembled. Ribosomal RNA (rRNA) is encoded in DNA regions forming parts of the nucleolus; it is the RNA of ribosomes or polyribosomes. Transfer RNA (tRNA) refers to short-chained RNA molecules of at least 20 types (one for each of the 20 amino acids in protein synthesis). tRNA combines with amino acids during protein synthesis and interacts with mRNA codons, thus providing a link between the information coded into nucleic acids and the amino acid sequence of proteins. Small nuclear RNAs (snRNAs) are small (about 90-300 nucleotides) chains in the nucleus that are involved in processing of mRNA and rRNA. Small cytoplasmic RNA (scRNA) functions primarily in the cytoplasm and forms the signal recognition particle. scRNA participates in the process of attaching ribosomes to the endoplasmic reticulum during synthesis of membrane proteins or proteins later secreted by the cell.

Ribonucleotide

A nucleotide in which a purine or pyrimidine base is linked to a ribose molecule. It is a component of RNA. See also Nucleotide

Ribosome

A small, sphere-shaped, cytoplasmic structures that is composed of RNA and protein and is the site of protein synthesis. Ribosomes are free in the cytoplasm and often attached to the membrane of the endoplasmic reticulum. Ribosomes exist in both eukaryotic and prokaryotic cells. Bacterial ribosomes are composed of two subunits: the smaller 30S subunit containing 21 proteins and a single 16S RNA molecule, and the larger 50S subunit containing 32 proteins and two RNA molecules (23S and 5S). 16S serves as a scaffold defining the positions of the ribosomal protein with the 3' end containing the anti-Shine-Dalgarno sequence. This sequence binds upstream to the

AUG start codon on the mRNA. 16S interacts with 23S and facilitates binding of 50S and 30S. Many antibiotic agents bind to the 30S and 16S subunits of the bacterial ribosome. This action inhibits translocation of peptidyl-tRNA from the A-site to the P-site and also causes misreading of mRNA, interrupting bacterial protein synthesis necessary for survival and reproduction.

Ribozyme

A nonprotein biological catalyst consisting of specific domains of ribonucleic acid (RNA) that can recognize, bind and digest nucleic acids thus playing a key role in intron splicing events. Several cleave precursors of tRNA resulting in functional tRNA while others act on rRNA. Ribozymes induce conformational changes which involve bringing the hydroxyl groups of RNA molecules into positions where their reactivity leads to hydrolysis and breakage of RNA chains. Ribozymes have been investigated as a potential therapeutic approach for diseases such as HBV infection, since their enzymatic activity can be used to block pathogenic protein synthesis. The utility of ribozymes as biologic and therapeutic agents has been limited due to their susceptibility to chemical and enzymatic degradation and to restricted target site specificity.

Rickettsiae

A diverse family of small, Gram-negative obligately intracellular bacteria found in ticks, lice, fleas, mites, chiggers and mammals. Examples include: genera Rickettsiae, Ehrlichia, Orientia and Coxiella. They are zoonotic pathogens that cause infections transmitted by invertebrate vectors.

RNA

See Ribonucleic Acid (RNA)

RNA Interference (RNAi)

RNA interference (RNAi) is an endogenous process of gene silencing that is due to interruption in the cell's translation. This interruption is triggered by the cell's own mRNA in response to the presence of and consequent destruction of matching double-stranded RNA sequences. Gene expression is inhibited in a sequence-dependent manner. The process endogenously protects the cell against viruses and other insults. The process has also emerged as a powerful gene silencing technique that is useful in research and development of therapeutics. See also Small interfering RNA (siRNA)

RNA Virus

A virus in which the genetic information is stored in RNA as opposed to DNA. The RNA is usually single-stranded although there are some that are double-stranded. human diseases caused by RNA viruses include Ebola, hemorrhagic fever, SARS, rabies, common cold, influenza, hepatitis C, West Nile fever, polio and measles.

RNAse

See Ribonucleases (RNAases)

S

Sarcoidosis

A rare multisystem inflammatory disorder characterized by chronic inflammatory granulomatous lesions (i.e., granuloma) in the lymph nodes and other organs. These granulomas are made up of epithelioid cells, macrophages, giant cells, fibroblasts and CD4+ T lymphocytes and their

formation occurs in response to immune response to poorly soluble antigen (e.g., mycobacteria or other pathogen) in genetic predisposed individuals. The most commonly affected sites are the lungs, lymphatic system, skin and eyes; the upper respiratory system, liver, bone marrow, spleen among other organs can also be affected.

SARS

See Severe Acute Respiratory Syndrome (SARS)

Sepsis

Systemic inflammatory response syndrome (SIRS) accompanied by a confirmed infectious process. See also Sepsis, Severe and Septic Shock and Systemic inflammatory response syndrome (SIRS)

Sepsis, Severe

A stage in the continuum of clinical response to infection defined as sepsis associated with organ dysfunction; sepsis associated with hypotension; or sepsis associated with hypoperfusion abnormalities. See also Sepsis and Sepsis, Severe and Systemic Inflammatory Response Syndrome (SIRS)

Septic Shock

A condition of clinical shock caused by endotoxin in the blood and characterized by hypoperfusion, multiple organ failure and persistent hypotension in a septic patient. See also Sepsis and Sepsis, Severe

Seroconversion

The development of detectable specific antibodies to a virus or other microorganism in the serum as a result of infection or immunization.

Serology

A blood test that detects the presence of antibodies to a particular antigen (e.g., rheumatoid factor, HIV test).

Serotype

The genotype of a unicellular organism that is defined by antisera against antigenic determinants expressed on the surface.

Severe Acute Respiratory Syndrome (SARS)

A respiratory disease of unknown etiology that apparently originated in Guangdong, possibly in November 2002, and was first reported at the beginning of 2003 in mainland China in 2003. It is characterized by fever and coughing or difficulty breathing or hypoxia and can be fatal. A novel, previously unknown coronavirus is associated with SARS and has been named "Urbani SARS-associated coronavirus" by WHO.

Single-Blind

A research testing parameter in which patients do not know which of several treatments they are receiving, thus preventing personal bias from influencing their reactions and study results.

Single-Nucleotide Polymorphism (SNP)

Single-nucleotide polymorphisms are the most common type of genetic variation. Each SNP represents a difference in a single nucleotide (e.g., a SNP may replace the nucleotide cytosine (C) with the nucleotide thymine [T]). SNPs occur approximately once in every 300 nucleotides. They are frequently found in the DNA between genes. SNPs can be used as biomarkers for diseases and may predict response to drugs and environmental factors (i.e., toxins).

siRNA

See Small interfering RNA (siRNA)

Steroids

A large family of compounds derived from cholesterol which are structurally similar in that they contain the tetracyclic cyclopenta[a]phenanthrene skeleton. Examples include plant and animal hormones, body constituents and drugs.

Syncytia

Large multinucleated cellular aggregates resulting from fusion of cells.

T

T Cell

One of two major classes of lymphocytes that develop in the thymus. T cell lineage markers are the expression of two T cell antigen receptors (TCR-1gammadelta and TCR-2alphabeta). TCR-2+ cells are further classified into two nonoverlapping populations that express the CD4 marker and help or induce immune responses (Th cells) or carry the CD8 marker and are predominately cytotoxic (CTLs). In general, CD4+ and CD8+ T cells recognize specific antigens in association with MHC class II and I molecules, respectively. CD4+ T cells can be further divided into Th0, Th1, Th2 and Th3 cells based on their cytokine production profile.

T Cell Antigen Receptor (TCR)

Cell surface receptor on T cells made up of a disulfide-bridged heterodimer, which recognizes processed antigen associated with an MHC molecule. Several polypeptides that form the CD3 complex associate to the TCR and are involved in TCR expression and signal transduction. Four different gene loci (alpha, beta, gamma and delta) encode the antigen-binding part of the TCR heterodimer and define the two types of TCR: TCR-2alphabeta and TCR-1gammadelta. Only one single type of TCR is expressed on a given T cell. TCR vaccines are under development for the treatment of rheumatoid arthritis.

T Helper Cell (Th)

MHC class II-restricted T cells expressing the CD4 marker. Depending on their cytokine profile, they are divided into Th0, Th1, Th2 and Th3 subsets. Th1 secrete IL-2 and IFN-gamma. Th2 secrete IL-4, IL-5, IL-6, IL-10 and IL-13. Th3 cells produce the immunosuppressor molecule, TGF-beta, and contribute to down-regulating the immune response. Th0 may secrete all of the above cytokines. See also Th0 Cell, Th1 Cell, Th2 Cell and Th3 Cell

T Suppressor Cell (Ts)

A T cell with no unique marker that downregulates function of other T and B cells and antigen presenting cells (APCs). TGF-beta-secreting Th3 cells and/or CTL cells may actually be responsible for this suppressor activity.

Th0 Cells

A T helper cell population from which Th1, Th2 and Th3 subsets are thought to develop. Th0 cells represent a less differentiated T cell population whose commitment towards Th1, Th2 or Th3 is determined by several factors, including the cytokine environment or the type of APC that activates the cell.

Th1 Cell

A T helper cell expressing the CD4 marker that produces IFN-gamma and IL-2 and promotes cell-mediated immunity. Th1 cells recognize antigen associated with class II MHC molecules and mediate inflammatory reactions. These cells are effective against intracellular pathogens such as viruses, bacteria and parasites.

Th2 Cell

A T helper cell expressing the CD4 marker that produces IL-2, IL-4, IL-5, IL-10 and IL-13. These cytokines enhance humoral responses by helping B cells in the production of different classes of immunoglobulins (Igs). Th2 cells are important in eliciting both antibody-mediated cytotoxicity against extracellular parasites and antibody responses against viral proteins.

Th3 Cell

A T helper cell expressing the CD4 marker and producing TGF-beta that strongly inhibits immune responses by suppressing B and T cell proliferation. These cells may be partly responsible for the activity attributed to T suppressor (Ts) cells.

Thrombocytopenia

A condition characterized by a decrease in the number of platelets in the blood. This can result in increased bleeding and decreased clotting.

Thymosin beta-4

An actin binding protein. It is an interferon-induced peptide expressed in hematopoietic cells and it regulates actin cytoskeleton by preventing G-actin polymerization. It is involved in cell proliferation, differentiation and motility. It is cleaved into seraspenide which inhibits the entry of hematopoietic pluripotent stem cells into the S-phase.

Tolerance

The ability to endure unusually large doses of a drug or toxin. An acquired drug tolerance is a decreasing response to repeated constant doses of a drug or the need for increasing doses to maintain a constant response.

Toll-Like Receptor 3 (TLR3)

A member of the toll-like (TLR) receptor family which includes key recognition structures of the innate immune system. When activated TLRs initiate production of inflammatory cytokines, chemokines, tissue destructive enzymes and type I interferons (IFNs). TLR signaling is also involved in activation of the adaptive immune system via upregulation of costimulatory molecules of antigen presenting cells (APCs). TLRs therefore can link innate and acquired immune responses. TLR3 has been shown to be expressed in the brain with significantly increased levels observed in the brains of patient's with Alzheimer's disease (AD). Studies have also shown that TLR3 may mediate the amyloid beta-induced activities of innate immunity in the neurodegenerative processes of AD.

Toll-Like Receptors (TLRs)

A class of single membrane-spanning, non-catalytic receptors that are a type of pattern recognition receptor (PRR). They are the key recognition structures of the innate immune system that recognize molecules shared by pathogens but distinct from host molecules. When activated, they initiate the production of inflammatory cytokines, chemokines, tissue degrading enzymes and type I interferons (IFNs). TLR signaling is also involved in activation of the adaptive immune system via upregulation of costimulatory molecules of antigen presenting cells (APCs). TLRs therefore can link innate and acquired immune responses. TLR signaling is thought to be involved in the pathogenesis of rheumatoid arthritis. Signaling via TLR7 has been shown to markedly induced IFN-alpha which enhances Th1-mediated cellular antiviral and antitumor immunity. TLR7 agonism has been shown to be effective in the treatment of actinic keratosis. TLR3 has been shown to be expressed in the brain with significantly increased levels observed in the brains of patients with Alzheimer's disease (AD). TLR4 is the main receptor for bacterial endotoxin and is a potential target for the treatment of sepsis. It has also been identified as a potential risk factor for asthma. TLR9 agonists have been developed that enhance anthrax vaccines.

Trachea

The air passage responsible for conveying air to and from the lungs that extends from the larynx into the thorax, where it branches into the right and left main bronchi.

Transcription

The process by which genes are copied into RNA, resulting in three major RNA types that interact in protein synthesis: messenger RNA (mRNA), ribosomal RNA (rRNA) and transfer RNA (tRNA). See also Ribonucleic Acid (RNA)

Transcription Factors

Endogenous substances (usually proteins) that bind to the promoter regions of genes and regulate the start, stimulation or termination of the genetic transcription process. Examples include NF-kappaB, nuclear factor of activated T cells (NF-AT), activator protein-1 (AP-1), CREB and signal transduction-activated transcription factors (STAT).

Transgenic

Refers to an organism in which gene(s) or DNA from another organism were incorporated via injection into the nucleus of the ovum. The resulting transgenic animal expresses the protein(s) that the new gene(s) encodes.

Translation

Protein synthesis resulting from the interaction of mRNA, rRNA and tRNA transcribed in the nucleus. The genetic code or sequence of nucleotides in mRNA is translated into a sequence of amino acids during polypeptide assembly. During translation, ribosomes read along the mRNA molecule, gradually assembling a corresponding amino acid sequence. Nucleotides are read three at a time as codons.

Tropism

Movement of an organism in response to an external source of stimulus (e.g., toward or away from the stimulus).

Tumor Necrosis Factor (TNF)

A group of cytokines that includes TNF-alpha, released by activated macrophages and lymphocytes, and TNF-beta, released from cytotoxic T lymphocytes (CTLs). The TNF family of receptors are important mediators of cellular immune responses including proliferation, differentiation, apoptosis and cytokine production.

Tumor Necrosis Factor-alpha (TNF-alpha)

TNF-alpha is a proinflammatory cytokine (also known as cachectin) and member of the TNF family of cytokines that is released by activated macrophages and lymphocytes. It acts via receptors belonging to the TNF family of receptors, among which TNF receptor 1 and 2 (TNFR-1, TNFR-2) trigger several signal transduction pathways, resulting in the activation of transcription factors such as NF-kappaB and cFos/cJun. TNFR-1 (also known as CD120a; p55/60) is expressed in most tissues and is fully activated by both the membrane-bound and soluble trimeric forms of TNF. TNFR-2 (also known as CD120b; p75/80), however, is found only in cells of the immune system and is activated by the membrane-bound form of the TNF homotrimer. Activated factors induce the transcription of antiapoptotic, proliferative, immunomodulatory and inflammatory genes. NF-kappaB is the major survival factor in preventing TNF-alpha-induced apoptosis and inhibition of this transcription factor may improve the efficacy of apoptosis-inducing cancer therapies; TNF-alpha-targeted therapies are also being tested in the regional treatment of locally advanced soft tissue sarcomas and metastatic melanomas. In addition, TNF-alpha-induced insulin resistance is believed to be a major contributor to the development of type 2 diabetes in obesity and elevated brain levels of TNF-alpha have been observed in Alzheimer's Disease (AD) and ischemic stroke patients. TNF-alpha is also a crucial cytokine in the establishment and maintenance of inflammation in multiple autoimmune diseases. Studies have reported elevated TNF levels at the site of active MS lesions in postmortem brain samples from patients with MS and CSF and serum TNF levels in individuals with MS are elevated compared to unaffected individuals with TNF levels correlating to the severity of the lesions. In addition, peripheral blood mononuclear cells from MS patients just prior to symptom exacerbation display increased TNF secretion after stimulation as compared to cells from the same patients during remission and inhibition of the TNF-alpha signaling pathway (e.g., TNF-alpha blockers, blockers of p38, JNK and/or ERK kinases, antagonists of transcription factor NF-kappaB activation) is a viable therapeutic strategy for the treatment of Crohn's disease, psoriasis, psoriatic arthritis, uveitis, sarcoidosis, Behcet's syndrome, graft versus host disease and ankylosing spondylitis.

U

Upstream

The nucleotide sequences in DNA or RNA that precede the codons specifying the mRNA for transcription or the protein coding sequences for translation. It is also used to describe events that occur early on within sequential reactions. See also Downstream

V

Vaccine

Any preparation intended for active immunological prophylaxis or therapy. Routes of administration include inoculation, ingestion and nasal spray.

Viral Envelope Proteins

Layers of protein which surround the capsid in animal viruses with tubular nucleocapsids. The envelope consists of an inner layer of lipids and virus-specific proteins also called membrane or matrix proteins. The outer layer consists of one or more types of morphological subunits called peplomers which are glycoproteins and project from the viral envelope.

Viral Shedding

The expelling of virus particles from the body, one route for which is through the respiratory tract. Virus shedding is an important means of transmission, although evidence of virus shedding does not necessarily equate transmissibility.

Viremia

The presence of viruses or viral particles in the circulation.

Virion

A single virus particle that includes the viral coat or envelope.

Virulence

The disease-producing ability of an infectious organism.

Virus

A small infectious particle between 10 and 300 nm in diameter, not visible with a light microscope. Viruses have no cell structure and thus differ from other infectious agents or cells. They have no wall and the genetic material is contained in either DNA or RNA encased within a protein shell or capsid. Some viruses may also have an outer membrane composed of lipoprotein. They are obligate parasites and need to enter a plant or animal cell in order to reproduce. Their RNA or DNA encodes for various proteins which are made by the host cell.

Vomiting

See Emesis

W

West Nile Virus (WNV)

The flavivirus first discovered in the West Nile area of Uganda and now spreading from tropical and subtropical areas to more temperate regions. WNV is a small, single-stranded RNA virus of approximately 40-50 nm in size and has a host-cell derived lipid envelope enclosing an icosahedral nucleocapsid core of 30-35 nm.

Wild-type

The normal, nonmutated version of a gene. Also the parent strain of a virus, bacteria, mouse, or other laboratory organism that are found in the wild.

X

Y

YLD

Acronym for "Years Lost due to Disability" which is calculated by the number of years lived in a condition multiplied by a disability weight for that condition assigned on a scale from 0 (perfect

health) to 1 (death). YLD = number of incident cases in reference period x disability weight x average duration of condition.

YLL

Acronym for "Years of Life Lost" which is calculated by the number of deaths multiplied by the standard life expectancy at the age at which death occurs. YLL = number of deaths + standard life expectancy minus age of death.

YPLL

An acronym for "Years of potential life lost" which is also known as potential years of life lost (PYLL). YPLL is a statistic that is a measure of premature mortality. It is an estimate of the average years a person would have lived if he or she had not died prematurely and therefore can it indicate the impact of various diseases and other lethal factors on a population.

Z

Zoonotic

A disease of animals that may be transmitted to humans.

Suggested reading

Related websites

- Centers for Disease Control and Prevention (CDC) – 2019 novel coronavirus, Wuhan, China - <https://www.cdc.gov/coronavirus/2019-ncov/index.html>
- Centers for Disease Control and Prevention (CDC) – SARS information - <http://www.cdc.gov/sars/index.html>
- MEDLINEplus: Coronavirus infections - <http://medlineplus.gov/coronavirusinfections.html>
- Middle East respiratory syndrome coronavirus (MERS-CoV) (World Health Organization) - <http://www.who.int/emergencies/mers-cov/en/>
- National Institute of Allergy and Infectious Diseases - <http://www.niaid.nih.gov>
- NCBI web resource: Severe Acute Respiratory Syndrome (SARS) - <http://www.ncbi.nlm.nih.gov/genomes/SARS/SARS.html>
- SARS information - Health Canada - <http://www.hc-sc.gc.ca/hc-ps/dc-ma/sars-sras-eng.php>
- World Health Organization – SARS information - <http://www.who.int/csr/sars/en/>

Related articles

- SARS Reference by B.S. Kamps and C. Hoffman (Eds.) - <http://sarsreference.com>
- 2019 Novel coronavirus (2019-nCoV) (New England Journal of Medicine) - <http://www.nejm.org/coronavirus>

Guidelines

[Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus \(MERS-CoV\) infection is suspected - Interim guidance \(World Health Organization, 2019\)](#)

[Clinical management of severe acute respiratory infection when novel coronavirus \(nCoV\) infection is suspected - Interim guidance \(World Health Organization, January 12, 2020\)](#)

[Infection prevention and control during health care for probable or confirmed cases of novel coronavirus \(nCoV\) infection - Interim guidance \(World Health Organization, May 6, 2013\)](#)

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[Interim guidance document: Clinical management of severe acute respiratory infections when novel coronavirus is suspected: What to do and what not to do \(World Health Organization, 2013\)](#)

[Management of asymptomatic persons who are RTPCR positive for Middle East respiratory syndrome coronavirus \(MERS-CoV\) - Interim guidance \(World Health Organization, January 2018\)](#)

[Treatment of MERS-CoV: Information for clinicians - Clinical decision-making support for treatment of MERS-CoV patients \(Public Health England, July 2014\)](#)

[Update on the epidemiology of Middle East Respiratory Syndrome coronavirus \(MERS-CoV\) infection, and guidance for the public, clinicians, and public health authorities - January 2015 \(Centers for Disease Control and Prevention, January 30, 2015\)](#)

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Related Information	Count
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