Early July saw the World Health Organization announce that the last known case of human severe acute respiratory syndrome (SARS) had been detected on 15 June. The elapsed time without further cases – more than two incubation periods – is an indication that this current SARS `epidemic' may be coming to an end. Despite this positive news, the then WHO Director-General Gro Harlem Brundtland warned that SARS could return and that a great deal of work lies ahead in order to clearly understand this disease. To this end, the WHO has outlined its public health research priorities before the winter flu season. They are:

- to understand if there is a potent risk for the disease to re-emerge from an animal reservoir;
- to aid the development of rapid diagnostic tests that work in the hospital setting to quickly distinguish between SARS and flu;
- to understand the reasons for the success and effectiveness of the control measures in China (where a relatively small number of healthcare workers were affected, with an apparently very low case fatality).

Efforts to develop drugs and vaccines should not be stopped, but the WHO sees this as a long-term investment.

So which companies are part of the search for a vaccine or potential drug treatment for SARS? In this article, we look at the range of activity, which runs the whole gamut from agents already marketed for other indications to those revived from suspended development.

**Pharma Industry Joins Efforts to Find SARS Treatments**

In April 2003, US Secretary of Health and Human Services (HHS) Tommy Thompson requested that pharmaceutical companies provide samples of any compounds they had that may be effective against SARS to the US National Institutes of Health (NIH). The NIH is currently testing approximately 2000 antiviral compounds in an aggressive screening program to identify potential treatments for SARS. In addition, a number of companies have recently announced that they are developing novel agents to treat SARS infections [see table 1]. However, the majority of these agents are still undergoing preclinical evaluation and, even with the US FDA and other regulatory bodies expediting the development and approval process, are unlikely to be commercially available in the near future. Thus, the best hope in the immediate future may lie in antiviral agents that are already approved, and have been extensively tested, for other viral diseases.

Thymalfasin (Zadaxin®) is the synthetic version of thymosin-α-1, a polypeptide (protein fragment) found naturally in the circulation and produced in the body’s thymus gland. Zadaxin is an immunomodulator that stimulates the immune system’s T cells and natural killer cells. Zadaxin is registered in over 20 countries, principally for the treatment of hepatitis B and hepatitis C virus infections, and as a vaccine adjuvant. In May, SciClone Pharmaceuticals, Inc. reported that SARS-related export sales to China were expected to drive sales of Zadaxin to more than $US15 million for the second quarter of 2003. This compares to revenues of $US5 million for the first quarter of 2003 and $US4 million reported for the second quarter of 2002.

Several compounds that are already in clinical studies for other indications have been identified as potential treatments for SARS. Hemispherx Biopharma, Inc. has several programs targeting SARS with the use of its lead compounds Alferon N Injection® and Ampligen®, a mismatched, double-stranded RNA experimental product acting potentially as an immunomodulator and antiviral. The programs assess the effects of Alferon N and Ampligen, alone or in combination, against the SARS coronavirus. NIH-sponsored studies of potential therapies for SARS have identified Ampligen as having unusually high and consistent antiviral activity against human coronavirus, the pathogen implicated as the causative agent of the disease. Ampligen demonstrated very high potency at very low concentrations (0.4 μg/ml) and had a favorable safety profile.

Another company hoping that the NIH will test its product is ImmuneRegen BioSciences, Inc., a
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biotechnology company engaged in the research and development of applications using modified substance P, a naturally occurring immunomodulator. The company has initially focused on developing its proprietary compound Homspera for the treatment of acute radiation syndrome (ARS) and acute respiratory distress syndrome (ARDS). Since it is the deterioration of the lung lining that causes people to die from pneumonia, ImmuneRegen researchers suggest that Homspera may have a role in treating SARS.

Pfizer Inc. has provided a number of experimental compounds to the US government for testing against coronavirus, including the rhinovirus protease inhibitor AG 7088 (rupintrivir). Pfizer had suspended clinical development of rupintrivir for the treatment of colds at the phase II stage. An article published online in *Science*

| Table 1. Drugs and vaccines under evaluation for use against SARS |
|---------------------------------------------------------------|
| **Product**        | **Company**                        | **Description**                                      | **Development status**                     |
| AG 7088 (rupintrivir) | Pfizer Inc.                        | Rupintrivir is a rhinovirus protease inhibitor; it is one of many compounds provided to the US government for testing | Development for rhinovirus infections suspended at phase II stage |
| Angiotensin II receptor antagonists | GenoMed, Inc. | Angiotensin II receptor antagonists (‘sartans’) may reduce mortality rate in patients with SARS | GenoMed is seeking volunteers for testing and has filed a patent application for the use of ‘sartans’ for SARS. |
| Anticoronavirus antibodies | Medarex, Inc./Massachusetts Biologic Laboratories | Fully human monoclonal antibody | |
| AVI-4179 (coronavirus antisense compound) | AVI Biopharma, Inc. | AVI-4179 is a NeuGene antisense compound targeting the SARS coronavirus. | Preclinical; AVI-4179 has been provided to NIAID for testing and to WHO-affiliated laboratories for cell culture and primate testing on a limited basis. |
| CEL-1000 | CEL-SCI Corporation | An immune-modulating peptide that appears to activate innate (very early stage) and Th1 type (cellular) immune responses to induce a broad-spectrum protection against infection in animal models | Preclinical; CEL 1000 and its analogs are being developed as potential injectable treatments for several indications, including malaria, infectious diseases, sepsis, cancers, allergies and autoimmune conditions. Its potential as a vaccine adjuvant is also being investigated. |
| Coronavirus inhibitors | ViroPharma Incorporated | ViroPharma is collaborating with USAMRIID to evaluate compounds from its chemical library for potential inhibitors of the SARS coronavirus | |
| Coronavirus vaccine | Antigen Express, Inc./Generex Biotechnology Corporation | Agreement in principle for vaccine development | |
| Coronavirus vaccine | GenVec, Inc. | Adenoviral vector vaccine | |
| Hepatitis C polymerase inhibitors | BioCryst Pharmaceuticals, Inc. | The compounds to be tested are novel, active site-directed inhibitors of the enzyme hepatitis C polymerase, which BioCryst developed in collaboration with Emory University and the French National Center for Scientific Research (CNRS). | Provided to NIAID for testing |
(13 May) suggested that inhibition of the viral protease may be the key to developing treatments for SARS, and that compounds such as AG 7088 may therefore form the basis for drugs that are effective against the disease.

**CombiMatrix Corporation** has produced pools of small interfering RNA (siRNA) molecules directed at specific genes of the SARS coronavirus. In collaboration with the US National Institute of Allergy and Infectious Diseases (NIAID) and the US Army Medical Research Institute of Infectious Disease (USAMRIID), the company is conducting initial screening of the siRNA samples against the SARS coronavirus. CombiMatrix’s microarray platform technology enabled the rapid preparation of customized siRNA molecules based on the published sequence of the SARS virus. The company’s researchers targeted two genes believed to be regulators of viral replication; an RNA-dependent RNA polymerase and a NTPase/helicase domain. The result was approximately 60 potential drugs. CombiMatrix has filed patents on the specific molecules that could become drugs against SARS. It plans to offer these drug candidates to partners to complete the preclinical and clinical development if these molecules, and others that CombiMatrix develops using its platform technology, show efficacy in initial tests.

### Table 1. Drugs and vaccines under evaluation for use against SARS

| Product               | Company                  | Description                                                                 | Development status                                                                 |
|-----------------------|--------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Homspera              | ImmuneRegen BioSciences, Inc. | A modified substance P that has shown in vitro activity against the coronavirus (substance P is a naturally occurring immunomodulator) | The company is seeking FDA permission to test Homspera in patients with acute respiratory distress syndrome and acute lung injury. |
| Interferon-α-n3 (Alferon N) | Hemispherx Biopharma, Inc. | Testing in collaboration with Genome Institute of Singapore | Ampligen is awaiting approval for use in the treatment of chronic fatigue syndrome in the EU and Canada, and is in phase III trials for this indication in the US. It is also being evaluated in studies involving patients with HIV, hepatitis B virus infection, malignant melanoma and renal cancer. |
| Mismatched double-stranded RNA (Ampligen) | Hemispherx Biopharma, Inc. | Testing in collaboration with Genome Institute of Singapore | |
| Leukocyte interleukin injection (Multikine™) | CEL-SCI Corporation | An immune adjuvant (comprising a natural mixture of human cytokines) with direct antiviral and anticancer activities that assists in host immune response reconstitution. | CEL-SCI has completed all phase II clinical trials of Multikine in patients with head and neck cancer. The drug is also be evaluated in breast, cervical and prostate cancer. |
| Ranpirnase             | Alfacell Corporation      | Alfacell has provided ranpirnase to the US federal SARS testing program | Ranpirnase (Onconase) is in phase III of development for mesothelioma and in phase II studies for prostate and renal cancer in the US. |
| SARS-specific small interfering RNA (siRNA) molecules | CombiMatrix Corporation | The company is collaborating with the NIAID and USAMRIID to conduct initial screening of the siRNA molecules against the SARS coronavirus | |
| Thymalfasin (Zadaxin)  | SciClone Pharmaceuticals, Inc. | An immunomodulator that stimulates the immune system’s T cells and natural killer cells. | |

Source: R&D Insight (Adis International)
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CEL-SCI Corporation is another company co-operating with NIAID and USAMRIID. It has signed an agreement with both institutes to test CEL-1000, an immune-modulating peptide, against a number of infectious diseases including SARS. The testing will be conducted to determine whether CEL-1000 could be used as a potential treatment and/or preventive agent against this disease.

AVI BioPharma, Inc. is also working with the NIAID. The company has provided an experimental NeuGene® antisense drug, which is targeted against the SARS coronavirus, to the NIAID for laboratory testing.

Vaccination Another Possibility
Secretary Thompson also met with major vaccine manufacturers GlaxoSmithKline, Wyeth, Merck & Co. and Aventis-Pasteur in April to urge them to test their vaccines against coronaviruses. There are also several companies developing novel vaccines against the SARS virus [see table 1].

GenVec, Inc. has formed a Collaborative Research and Development Agreement (CRADA) with the Vaccine Research Center at NIAID (VRC/NIAID) to develop a vaccine for SARS using the company’s proprietary adenoviral vector technology. The CRADA will be complementary to the funded contract with the VRC/NIAID to construct and produce an adenovirus-based SARS vaccine. The agreement will govern a preclinical collaboration to evaluate and develop adenoviral vectors expressing modified SARS genes; the VRC/NIAID will test the preclinical vaccine candidates in preclinical models.

Another vaccine is in preclinical development with Generex Biotechnology Corporation and Antigen Express, Inc. This vaccine will utilize Generex’ proprietary depot drug delivery and formulation technologies and Antigen Express will contribute its proprietary Ii protein suppression and Ii-Key peptide vaccine-enhancing technologies. Antigen Express is

| Company | Product/platform | Development status |
|---------|-----------------|-------------------|
| Abbott Laboratories, artus GmbH | A real-time PCR diagnostic test that produces results within 2 hours. From that test, artus has developed a ready-to-use system (RealArt HPA-Coronavirus RT PCR Reagents). | Launched in Asia and Europe in April. |
| Beijing Genome Institute | A 1-hour test for SARS, based on the sequenced genome; the test uses a particular protein produced by the virus, which reacts with an antibody produced by SARS patients. | Research teams in Beijing, Canada and Singapore are using the microarray to search for novel protein biomarkers, which will then be used in a rapid diagnostic test. If successful, therapeutic and/or vaccine strategies based on insights provided from these biomarkers may be pursued as well. |
| Ciphergen Biosystems, Inc. | A SARS microarray developed using its ProteinChip® technology. | |
| CombiMatrix Corporation | DNA microarrays for SARS based on its Lab-on-a-Chip technology. | CombiMatrix plans to release three types of microarrays including one for detection and screening. |
| EraGen Biosciences, Inc. | SARS-specific assay test developed with EraGen’s Gene-Code™ technology. | The test is being evaluated by USAMRIID and was shipped to the WHO Central Public Health Laboratory (UK) and the British Columbia Center of Disease Control in April. |

**Table 2. SARS tests in development**
developing novel therapeutic vaccines for cancer and infectious diseases. Its platform technologies greatly enhance T-helper cell responses, resulting in strong antibody and cytotoxic cellular responses. T-helper cells also mediate immunological memory – key to developing long-term, disease-free responses. In June, Generex announced an agreement in principle to acquire all shares of the privately owned Antigen Express in exchange for Generex shares.

**Therapeutics Only Half the Story**

As evidenced by the WHO’s commitment to the development of rapid diagnostic tests, quick and accurate detection of SARS is the other half of the story. Frost & Sullivan analyst Annabel Entress commented that “the sales of SARS diagnostics are not expected to act as a long term revenue generator for the diagnostics industry”. In fact, Roche is expecting to make just $US10 million from its test. Although the potential revenues are small compared with those from HIV/AIDS, for example, “companies have still rushed to the forefront of discovery diagnostics”, noted Entress. Globally, over 30 companies are currently working on SARS diagnostics; some of these companies are listed in table 2.

In mid-May, *Abbott Laboratories* commenced a worldwide marketing and distribution agreement with *artus GmbH* for what is believed to be the first commercial PCR-based test to detect a form of the coronavirus linked to SARS. Hamburg-based biotechnology company artus developed the virus detection assay together with the Bernhard-Nocht Institute of Hamburg, Germany. The institute was part of WHO’s research network that identified the virus causing SARS. Based on the discovered genetic sequence, the Bernhard-Nocht Institute developed a real-time PCR diagnostic test that produces results within 2 hours. From that test, artus developed a ready-to-use system (RealArt™ HPA-Coronavirus RT PCR Reagents), which was launched in Asia and Europe in

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**Table 2. SARS tests in development**

| Company                           | Product/platform                                                                 | Development status                                                                 |
|-----------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Focus Technologies Inc.           | A first-generation real-time PCR test that detects the coronavirus associated with SARS via reverse transcription of specific viral genomic RNA sequences followed by PCR amplification. | Focus is using the test in its reference laboratory to help clinicians diagnose disease in patients with suspected SARS. |
| Prodesse, Inc.                    | A PCR assay based on the company’s Hexaplex® platform. Hexaplex is an assay system for respiratory illnesses that simultaneously detects the seven most common lower respiratory viruses. The test targets three independent sections of the SARS genome. Because SARS is the third major subtype of coronavirus that infect humans, the test is designed to detect the two other subtypes of human coronavirus (OC43 and 229E); this will help distinguish between SARS and ‘normal’ coronavirus infections. | Prodesse completed the development of its SARS/Coronaplex assay in mid-June; kits have been shipped to China and Taiwan. |
| Roche Diagnostics, Genome Institute of Singapore | A SARS diagnostic test based on Roche’s PCR technology. | Roche plans to launch a diagnostic test by end-July; Genome Institute of Singapore has already started developing a primer set for real-time PCR detection. |
| Vaxim, Inc.                       | A peptide (V-S26) synthesized from SARS viral proteins. | Vaxim has successfully integrated V-S26 with the company’s proprietary carrier platforms to develop a SARS point-of-care test kit, named V-ST11. |

Source: R&D Insight (Adis International)
mid-April. Under the terms of the deal, artus will manufacture the test and Abbott will market and distribute it, initially for use in North America, the UK, Germany, and Austria. Abbott will also help artus submit the test to the FDA and will market and distribute it through its molecular diagnostics alliance with Celera Diagnostics.

In June, Vaxim, Inc. identified and synthesized a peptide from SARS viral proteins, named V-S26, which is confirmed to bind specifically with serum antibody from SARS-recovered patients. Vaxim has also successfully integrated V-S26 with the company’s proprietary carrier platforms to develop a SARS point-of-care test kit (named V-ST11). The test only takes 10–15 minutes to perform, in contrary to existing testing methods employing traditional technologies that take over 2 hours. The V-ST11 test requires much less time and has the major advantage of being safe by using synthetic peptides for capturing SARS antibodies instead of requiring the use of SARS proteins or virus, which can be highly contagious. Vaxim is also looking to apply this new technology in developing promising vaccine and therapeutic solutions for SARS.

In mid-June, Prodesse, Inc. completed development of a molecular test based on its multiplexing technology for the detection of the coronavirus causing SARS. The SARS/Coronaplex™ assay detects the SARS virus by analyzing a patient sample for the presence of the genetic material of the SARS virus. According to Chief Science Officer Dr Kelly Henrickson, “it is particularly difficult to design a gene-based test for newly discovered organisms such as the SARS virus because of the lack of genetic data from a large number of organisms. Any test that fails to take this into account may ultimately be ineffective in detecting a broad range of clinical isolates, resulting in false negative results.” As a consequence, Prodesse has used its multiplex technology to target three independent sections of the SARS genome. Given that SARS is the third major subtype of coronavirus known to infect humans, the test has also been designed to detect the two other subtypes of human coronavirus, known as OC43 and 229E. “This capability will help clinicians distinguish between SARS and ‘normal’ coronavirus infections”, explained Dr Henrickson.

In July, Roche Diagnostics announced the worldwide launch of its SARS diagnostic product; the test is for research use only. The test was developed over an 8-week period following the May deal between Roche Diagnostics and the Genome Institute of Singapore to jointly develop a SARS detection kit based on Roche’s polymerase chain reaction (PCR) technology. The institute has already begun work on developing a primer set for real-time PCR detection on the Roche LightCycler® system. The Genome Institute of Singapore is one of the institutes that sequenced the SARS genome.

**What is Severe Acute Respiratory Syndrome?**

Severe acute respiratory syndrome (SARS) is a respiratory illness that has recently been reported in Asia, North America and Europe. Scientists at the US CDC and other laboratories have detected a previously unrecognized coronavirus in patients with SARS. The new coronavirus is the leading hypothesis for the cause of SARS.

In general, SARS begins with a fever greater than 100.4°F (≥38.0°C). Other symptoms may include headache, an overall feeling of discomfort, and body aches. Some people also experience mild respiratory symptoms. After 2–7 days, SARS patients may develop a dry cough and have trouble breathing. No treatment beyond good intensive and supportive care has been consistently shown to improve prognosis.

The primary way that SARS appears to spread is by close person-to-person contact. Most cases of SARS have involved people who cared for or lived with someone with SARS, or had direct contact with infectious material (e.g. respiratory secretions) from a person who has SARS. It also is possible that SARS can be spread more broadly through the air or by other ways that are currently not known.

Source: US Centers for Disease Control and Prevention