Canadian SARS Research Consortium

Report 2003–2005

A Framework for a Canadian Rapid Research Response

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A Framework for a Canadian Rapid Research Response

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Fonds de la recherche en santé Québec

Michael Smith Foundation for Health Research

CANVAC

Canadian Network for Vaccines and Immunotherapeutics

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TABLE OF CONTENTS

Foreword

Dr. Bhagirath Singh, Ph.D.
Scientific Director
CIHR Institute of Infection and Immunity

Severe acute respiratory syndrome (SARS) hit several countries, including Canada, in late 2002 and early 2003. By late March 2003, the disease was spreading in Toronto and time was of the essence in developing a research strategy to complement other public health actions taken to address the disease outbreak. The medical community and general public needed to know: What causes SARS? How can the infectious agent be detected? How can transmission be prevented? What are the most effective treatments for SARS patients? When will a SARS vaccine be available? Canadian scientists quickly responded — a team of researchers from Vancouver, Winnipeg and Toronto was the first to sequence the genome of human SARS coronavirus — the virus now known to cause SARS. But this information alone was not enough to prevent the spread of SARS or to treat SARS patients.

The Canadian Institutes for Health Research (CIHR) Institute of Infection and Immunity responded by launching a request for proposals for research to detect the SARS virus, develop treatments, and develop a human SARS vaccine. This initiative was to complement work being carried out in federal and provincial government institutions. In contrast to the usual grant cycle of more than one year, it was within only a few weeks of full peer review that four proposals were funded, creating early momentum for SARS research in Canada. Providing funds rapidly posed a significant challenge, because granting agencies do not usually have money available to fund emergency programs. The Institute of Infection and Immunity initially launched the request for proposals with $250,000 from its own development grant and rapidly established partnerships with various stakeholders, so that the funds available to the successful applicants grew to a total of $1.7 million. Further requests for applications in social, behavioural and public health issues concerning SARS were launched by other CIHR institutes and partners and funded in early 2004.

To develop a cohesive research program, the CIHR and its Institute of Infection and Immunity played a leadership role in establishing the Canadian SARS Research Consortium (CSRC) in June 2003. Composed of individuals from the scientific, medical and business communities and from funding bodies and public health agencies, the CSRC identified gaps and coordinated the SARS research effort. The purpose of this report is to provide a factual summary of the organization and activities of the CSRC, to highlight some of its accomplishments and to outline the lessons learned and steps that are being taken to develop a permanent network, modeled on the CSRC, to provide a rapid research response in future infectious disease outbreaks.

Researchers identified and funded by the CSRC made significant contributions to understanding SARS. In fact, many of the initial questions posed by the medical community and public have been answered. For example, promising results of a clinical trial of a therapy for SARS patients have been reported and

three candidate human vaccines have been developed. The results have been communicated to the scientific and medical community in journal publications and at international scientific meetings and to the general public in several hundred media interviews given by members of the Consortium and SARS researchers.

Fortunately, the spread of SARS was halted in the summer of 2003, due to a massive public health effort. It is not known whether SARS will return, but the SARS outbreaks highlighted the need for a permanent network to coordinate a rapid research response to emerging infectious diseases. The SARS experience has taught us that it is very difficult to establish such a network during a health crisis. Therefore, the CIHR Institute of Infection and Immunity has created the Canadian Rapid Research Response Team (C3RT), consisting of government health agencies, funding agencies, infectious disease researchers, international agencies and members of the private sector. The mandate of the C3RT is to rapidly mobilize Canada's health research community to address specific research questions posed by new infectious agents in a coordinated and focused manner.

I would like to thank the CIHR for its support during the SARS crisis and its continuing support of our initiatives. I am grateful to Dr. Alan Bernstein, president of CIHR, for his insight in the creation of CSRC. I also thank Dr. Mark Bisby and my fellow scientific directors, particularly Drs. John Frank, Morris Barer, Bruce McManus and Phil Branton, for their timely advice and support of the SARS research initiative.

I am indebted to the members of the peer review committees, Management Group and Scientific Advisory Committee for their guidance, dedication and contributions to the CSRC and its initiatives. I would also like to thank the staff of the Institute of Infection and Immunity for their support of the Consortium activities. Mr. Bruce Moor helped with the peer review and funding issues for SARS grants. Ms. Tess Laidlaw and Ms. Janet Weichel McKenzie's efforts were invaluable in preparation of material and coordination of media relations. I would like to express my appreciation to Ms. Cheryl Holden and Dr. Michelle French for writing and editing this report. Thank you also to the media for helping the CSRC communicate SARS information to the public. I would like to thank the front-line health care workers for their tireless efforts, under very demanding conditions, in providing expert care to SARS patients and for helping to collect patient samples that have allowed researchers to make progress in understanding and treating SARS. Finally, I am grateful to Ms. Carol Richardson for running all operations of CSRC with the dedication and efficiency that has made this report possible.

EXECUTIVE SUMMARY

The Canadian SARS Research Consortium (CSRC) was formed to rapidly respond and mobilize Canada's health research community to address, in a coordinated and focused manner, research questions posed by emerging pathogens specifically resulting from the outbreaks of Severe Acute Respiratory Syndrome (SARS) in the spring of 2003.

The mandate of the CRSC is to coordinate, promote and support SARS research in Canada specifically in five areas: diagnostics, vaccine development, therapeutics, epidemiology and databases, and public health and community impact. The Consortium will also strive to develop international linkages and partnerships to strengthen the sharing of information and contribute to the enhanced control and eradication of SARS.

The CSRC is a coalition of funding agencies, public and private sector organizations and investigators with a primary interest in SARS research. The Consortium's Management Group facilitates collaboration among researchers and among research funders, nationally and internationally, to eliminate redundancy and encourage synergy through partnerships, with input from the Scientific Advisory Committee (SAC).

The CSRC mobilized and streamlined the Canadian SARS research effort by bringing together funding partners, eliminating duplication and developing more cooperative interaction among research groups. Research teams included clinical front-line workers who could use the results of research to improve diagnosis and start new clinical trials for therapeutic interventions during the SARS outbreaks.

Researchers funded by the CSRC have identified the cause of SARS, sequenced the SARS genome, developed sensitive assays to detect SARS in clinical samples, identified a potential therapy for SARS patients, determined which infected individuals have the best and worst prognosis and developed candidate human SARS vaccines. The results of their research have been presented at numerous scientific meetings and conferences and have resulted in 42 publications in scientific journals, with an additional 15 manuscripts submitted or in preparation. The new knowledge generated will allow health care workers to protect themselves and protect the health of Canadians, treat SARS patients more effectively should the disease re-emerge and prepare for future outbreaks of other infectious diseases.

The public was kept informed about SARS and research progress during the SARS outbreaks through numerous media interviews given by CSRC members and SARS researchers. CSRC members also provided information and made recommendations to the National Advisory Committee on SARS and Public Health, established in May 2003 by the Honourable Anne McLellan, Minister of Health to provide a "third party assessment of current public health efforts and lessons learned for ongoing and future infectious disease control".

In July 2003, human transmission of SARS ceased due to a massive public health effort. While SARS has not reappeared, except for a few contained incidents in Asia, it is but one example of a newly emerging infectious disease that has an adverse effect on human health. Scientists believe that the impact of SARS will be minor in comparison to the expected influenza pandemic or another, as yet unknown, infectious disease.

The National Advisory Committee on SARS and Public Health has stated that "there is an immediate need to strengthen Canada's public health system both in research and infrastructure". The Government of Canada responded by establishing the Public Health Agency of Canada (PHAC). The Committee also called for strategic investments in government public health science and the establishment of a permanent network, based in academia and the private sector, to broaden and deepen research response capacity. The Committee suggested that the Consortium could become a model for such a network and evolve into a more permanent structure to address newly emerging infectious diseases in Canada.

The CIHR Institute of Infection and Immunity has created the Canadian Rapid Research Response Team (C3RT), a permanent standing committee, to identify emerging health problems and assess if the problem may benefit from a rapid research response. The team consists of government health agencies, funding agencies, infectious disease researchers, international agencies and members of the private sector. The mandate of the C3RT is to rapidly mobilize Canada's health research community to address specific research questions posed by new infectious agents in a coordinated and focused manner.

INTRODUCTION

Historical context

Severe Acute Respiratory Syndrome (SARS) emerged as a new respiratory disease in China at the end of 2002 and quickly spread to several countries, including Canada, by the spring of 2003. The outbreak of SARS posed significant challenges for the world's public health system and front-line health care workers.

The Canadian SARS Research Consortium (CSRC) was created in June 2003 as a result of discussions within Canada's health research community, funding agencies and industry. Its objective was to address, in a rapid, coordinated and focused manner, specific research questions posed by SARS and to develop responses that addressed public needs.

CSRC Mandate

To coordinate, promote and support SARS research in Canada specifically in five areas: diagnostics, vaccine development, therapeutics, epidemiology and databases, and public health and community impact. The Consortium also strives to develop international linkages and partnerships to strengthen the sharing of information and contribute to the enhanced control and eradication of SARS. CRSC is a deliverables-driven network that establishes research priorities and clear objectives, coordinates funding and facilitates integration of the funded research projects.

CSRC Organization

The CSRC consists of a Management Group, a Scientific Advisory Committee (SAC), Executive Committee and a National SARS Research Team (Figure 1). Dr. Alan Bernstein, president of the Canadian Institutes of Health Research (CIHR), called together the first teleconference of the Consortium members and then moved to select Dr. Bhagirath Singh, Scientific Director of the CIHR Institute of Infection and Immunity (CIHR-III), as chair of the Management Group.

Management Group: The Management Group, chaired by Dr. Singh, facilitates collaboration among researchers and funding organizations both nationally and internationally, eliminates redundancy and encourages partnerships, establishes national research platforms, solicits participation from the biopharmaceutical industry and provides information and advice to the federal National Advisory Committee on SARS and Public Health. Members of the Management Group and their organizations funded, provided significant in-kind resources and/or continued to support research projects in several key areas. Figure 1 lists the Management Group members and Appendix 1 contains profiles of the individual organizations.

The Scientific Advisory Committee (SAC): The SAC is composed of members of the research community with expertise in the areas of virology, public health, diagnostics, vaccine development and immunology (Figure 1). The role of the SAC is to advise the Management Group on research strengths and weakness, recommend areas where further investigation could be advanced through the launching of requests for proposals or applications, identify opportunities for international collaboration and coordinate research programs within Canada to ensure an overall comprehensive approach to SARS research. At least one-third of the SAC members, while knowledgeable about scientific issues, are not directly involved in SARS research, nor do they benefit from research funding provided by the CSRC.

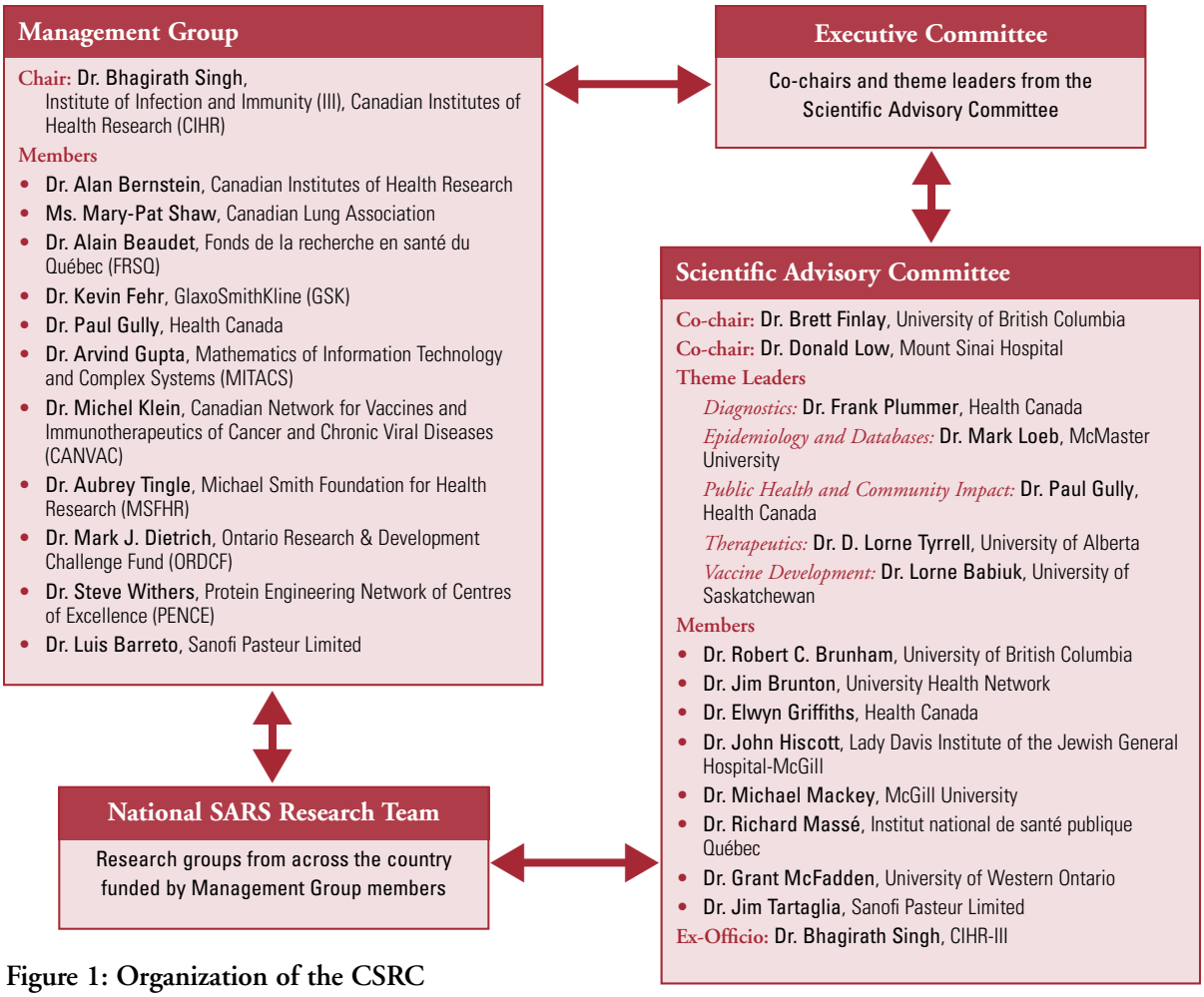

Figure 1: Organization of the CSRC

An early accomplishment of the SAC was to identify research areas or themes. In each area, theme leaders were appointed to: prepare an inventory of SARS research within their themes; determine research strengths and weaknesses; establish research priorities; document linkages in Canada and internationally; and recommend areas for development. The research themes established were: diagnostics, vaccine development, therapeutics, epidemiology and databases, and public health and community impact.

Executive Committee: This committee, consisting of the five theme leaders and the two SAC co-chairs, reports to the SAC to help guide scientific research regarding SARS.

The National SARS Research Team: The team consists of research groups funded by the participants in the Consortium. Many of these research groups were funded by grants awarded by CIHR in three separate requests for research proposals/applications and were financially supported by several Consortium members. In addition to these initiatives, Management Group members, including Health Canada, Canadian Network for Vaccines and Immunotherapeutics (CANVAC), Protein Engineering Network of Centres of Excellence (PENCE), and Mathematics of Information Technology and Complex Systems (MITACS) funded and supported research projects within their organizations. The Michael Smith Foundation for Health Research (MSFHR), with funds from the government of British Columbia, supported a SARS Accelerated Vaccine Initiative (SAVI) with the goal of developing a human SARS vaccine.

OUTCOMES

Identification of Research Priorities

The expertise of the members of the SAC in the areas of virology, immunology, public health and diagnostics was key to the success of the CSRC, as were their ability to assess research strengths and weakness and set clear objectives. The theme leaders and other members of the SAC provided essential comprehensive overviews of the ongoing research in Canada, which is especially important with emerging diseases such as SARS, where the research moves rapidly and no one group oversees all of the funding and research. The SAC helped the Management Group set SARS research priorities.

Funded Research

Research was funded in three areas:

- Led by CIHR, three separate requests for proposals/applications were launched, with successful applicants funded by several organizations in the Management Group (Table 1). With SARS I, the Consortium supported basic and clinical research. The SARS II grants supported public health and health care systems research, while SARS III grants focused on treatments for SARS. The rapid launch of SARS I by CIHR-III was a significant accomplishment. Within two months of the SARS outbreak in Toronto, four research groups had their applications approved. This rapid launch and compressed review time contrasts sharply with the typical grant funding cycle of 16 months and is a critical element in a timely response to rapidly emerging infectious diseases.

Table 1: SARS requests for proposals/applications launched by the CSRC members, area of research funded and funding partners

Funding competition	Area of research	Funding partners
SARS I Host Response to Severe Acute Respiratory Syndrome (April 2003) Funding: $1.7 million	To support research investigating the causes and consequences of severe acute respiratory syndrome	CIHR-III, CANVAC, CIHR, FRSQ, Health Canada, ORDCF and the University of Western Ontario
SARS II Public Health and Health Care System Preparedness and Response to SARS: Evaluations and Lessons Learned (September 2003) Funding: $1.6 million	To support research projects examining and analysing the recent public health and health care system responses to the SARS outbreak in Canada in the context of the global epidemic. Special emphasis is placed on ways to ensure that evidence-based practice, and cost-effective outbreak management strategies, are utilized to the maximum extent possible in any future outbreaks of this kind.	CIHR Institutes of: Population and Public Health (IPPH), Health Services and Policy Research (IHSPR), CIHR-III, Circulatory and Respiratory Health (ICRH), Aging (IA), the Lung Association, and Health Canada
SARS III GlaxoSmithKline Small Molecule Pilot Project Grants Initiative (October 2004) Funding: $750,000	To support pilot project research in the area of SARS biology and identification of small molecule targets as antiviral agents	CIHR, CIHR-III, CIHR/Rx&D Research Program and GlaxoSmithKline Inc.

- Individual organizations within the Management Group supported and performed research within their organizations. These included Health Canada, three Networks of Centres of Excellence (NCEs) and the MSFHR, which was supported by a grant from the British Columbia government in the form of SAVI (Table 2).

Table 2: Research supported within individual Management Group organizations

Organization	Research focus
Health Canada	To understand the epidemiology of SARS and to mathematically model and simulate the spread of infectious diseases
CANVAC	To understand patients' immune response to SARS and development of SARS vaccines
PENCE	To identify targets for therapy and therapeutic compounds for SARS and develop SARS vaccines
MITACS	To mathematically model and simulate the spread of infectious diseases to prevent and help control future infections
MSFHR and SAVI	To develop a human SARS vaccine as quickly as possible

- The SARS Patient Material Collection and Database Project: There is a great need among researchers for access to specimens from SARS patients and for an accompanying database of relevant clinical, epidemiologic, laboratory and, where applicable, pathological data. The Consortium is helping to facilitate the collection and sharing of patient samples. A SARS sample bank and registry was developed under the direction of Dr. Loeb at McMaster University in response to requests for blood from convalescent patients. SARS patients were contacted for permission to use their stored samples for research and for the collection of new blood samples. Banked samples will be catalogued and transferred to the National Microbiology Laboratory (NML) in Winnipeg. An inventory of existing patient samples, currently held at sites in Toronto, will also be developed. Investigators wishing to gain access to samples for research will send requests, complete with documentation of local ethics approval for the proposed project, to the NML. An NML scientific advisory committee will review the request for research merit and assign priority. Funding partners for this initiative include CIHR-III, MSFHR and Sanofi Pasteur Limited.

Research Results

Canadian researchers and clinicians have made significant contributions to our understanding of SARS. An early research success by Canadian clinicians and scientists from across the country, made simultaneously by another group, was the identification of the SARS coronavirus (SARS-CoV) as the cause of SARS. Viruses that are similar to SARS produce only mild, cold-like symptoms in humans, whereas infection with SARS-CoV can lead to severe respiratory symptoms and result in death in some individuals. Once it was known that SARS was caused by a virus, a collaborative team from the Michael Smith Genome Sciences Center, the BC Centre for Disease Control and the NML determined the genomic sequence of the virus. In fact, the short time from the World Health Organization (WHO) alert on SARS in March 2003 to the announcement by the Canadian research team of the full genomic sequence of the SARS virus in the journal *Science* in May 2003 is unprecedented in the history of infectious disease.

Sequencing the SARS genome, however, was only the first step in understanding the virus and combating it. Several key questions and goals remain and are being solved through research supported by the Consortium. These include:

- development of sensitive tests to detect the SARS virus in blood and other clinical samples;
- identification of specific groups of people at a higher risk of developing SARS;
- identification of biological targets for the development of therapies;
- rapid development of a human SARS vaccine;
- establishment of mathematical models of the spread of emerging infectious diseases to allow policy makers to test the impact of various types of interventions; and
- long-term effects of SARS-CoV on patients' health and the psychosocial impact of the disease on patients, health-care workers and non-SARS patients.

Some of the highlights of the research supported by the Consortium are summarized below, but much of the research is ongoing and results are not yet available.

SARS I—Host Response to Severe Acute Respiratory Syndrome: The CIHR-III, together with CANVAC, CIHR, the Fonds de recherche en santé du Québec (FRSQ), Health Canada, the Ontario Research and Development Challenge Fund (ORDCF) and the University of Western Ontario, funded four research teams to examine the severe lung disease caused by SARS, develop a rapid diagnostic test, engineer a vaccine and develop anti-SARS drugs.

During the first SARS outbreak, no tests were available to detect the virus, since SARS-CoV was a new virus. The research teams led by Dr. Michel Bergeron and Dr. Loeb have developed sensitive tests to detect the virus in clinical specimens. If SARS re-emerges, the tests developed by these teams and others will be essential for clinicians to be able to accurately diagnose the disease.

The research team led by Dr. Loeb was also engaged in numerous epidemiological and clinical research projects to determine how SARS was spread and how patients fought infection. Front-line health care workers were especially at risk for SARS. Several risk factors involved in the transmission of SARS from patients to health care workers were identified, including increased time spent in a patient's room, closeness to the patient's airway and lack of masks. This information is critical for protecting health care workers in the future.

Because SARS is caused by a virus, antibiotics are not useful in treating the disease and few effective treatments are known. Dr. Eleanor Fish of Dr. James Dennis's team developed a potential therapeutic treatment for SARS that, when tested, improved patient outcome. The group is working with the Global Influenza Programme Group to design treatment regimes that could be used in a future outbreak of SARS or influenza.

Dr. Danuta Skowronski's research group formed part of a large initiative to rapidly develop a human vaccine for SARS. The progress made in the development of candidate vaccines is discussed in the next section. The team has also developed diagnostic tests, including PCR and serologic neutralization assays, that were shared with other national and international agencies and used in vaccine evaluation in animals. The neutralization assay was also used in a survey of more than 400 health care workers who cared for patients with SARS to examine the possibility of further spread within British Columbia. This team also developed mathematical models to help explain the difference in SARS experience between Toronto and Vancouver. The results highlight the critical importance of the response to the first patient in determining the likelihood of an epidemic.

Further details on the successful principal applicants and summaries of the progress made by these groups are found in Appendix 2.

SAVI—SARS Accelerated Vaccine Initiative: Vaccination is a very effective way to protect people from infectious diseases. Developing a new vaccine, however, usually takes years. The SAVI research team, led by Dr. Brett Finlay and Dr. Robert Brunham, adopted emergency management techniques and a rapid and coordinated research response to quickly develop a SARS vaccine. The team has made three types of vaccine preparations and has tested them in animals. Although the number of cases of SARS in 2004 has been low, these vaccines will be available for human clinical trials should a major outbreak of the disease occur again. It is expected that the vaccine will have major benefits for high risk individuals, such as health care workers, airline employees and individuals at risk due to exposure to infected patients. The approach taken by SAVI can be highly effective when applied appropriately to new infectious diseases. A detailed summary of the work by SAVI is found in Appendix 3.

CANVAC: Knowledge of human immune responses to SARS infection is critical for the development of effective SARS vaccines and also to identify individuals who are most at risk of contracting the disease. The CANVAC research team defined, in infected individuals, the immune responses of those with a favourable prognosis. The team also identified parts of the SARS virus to which immune cells from patients reacted. These parts represent good choices for use as a SARS vaccine. The CANVAC team also has developed vaccine preparations and is currently testing them in animals. CANVAC's corporate collaborators were BD Biosciences, Beckman Coulter Inc., Berne Biotech Ltd. and TransGene. A detailed summary of the CANVAC research results is found in Appendix 4.

PENCE: PENCE scientists were, and continue to be, engaged in several projects that involve producing and studying key SARS proteins that allow the virus to infect cells or spread, as well as identifying molecules that inhibit the function of these proteins. These inhibitory molecules hold great promise as therapeutic compounds to prevent SARS infection or to treat the disease. Detailed summaries of the work of the PENCE researchers are found in Appendix 5.

MITACS: The MITACS team focused on the modeling and analysis of communicable diseases, forming collaborations with researchers from many disciplines, with strong support and participation from Health Canada. Successes include the development of a model for SARS transmission dynamics and a qualitative comparison of experiences in all major SARS-affected regions. The model indicates that a quick reaction, in the form of stricter hospital infection control protocols, is the most effective strategy for short-term containment of an epidemic such as SARS. A summary of this research is found in Appendix 6.

SARS II—Public Health and Health Care System Preparedness and Response to SARS: Evaluations and Lessons Learned: CIHR, the Lung Association and Health Canada launched this request for applications for research to examine and analyze public health and health care system preparedness and Canada's response to SARS. Goals include the identification, analysis and study of the social, ethical, psychological, economic and other consequences of the SARS outbreak. The information gained will allow public health and health care providers to respond optimally to future occurrences of SARS and other similar epidemics. The successful principal applicants and their research proposals are listed in Appendix 7. This research is ongoing and no results have been reported.

SARS III— GlaxoSmithKline Small Molecule Pilot Project Grants Initiative: The objective of this initiative is to support pilot projects in the area of SARS-CoV biology and identification of small molecule targets as antiviral agents. Applications have been received and grants will be awarded in March 2005.

Knowledge Translation to the Public

The public was kept informed about SARS and research progress during the SARS outbreaks through numerous media interviews given by CSRC members, including Dr. Singh, chair of the Management Group, Dr. Donald Low, co-chair of the SAC, other SAC members and SARS researchers. Members of the Consortium were key contacts for interested researchers and represented the CSRC at various meetings nationally and internationally. The research teams included clinical front-line workers who could use the results of research to improve diagnosis and start new clinical trials for therapeutic interventions during the SARS outbreaks.

The CSRC members also provided information and made recommendations to the National Advisory Committee on SARS and Public Health, established in May 2003 by the Honourable Anne McLellan, Minister of Health to provide a "third party assessment of current public health efforts and lessons learned for ongoing and future infectious disease control".

Recommendations of the National Advisory Committee on SARS and Public Health

The report by the National Advisory Committee on SARS and Public Health outlined the immediate need to "strengthen Canada's public health system in terms of research and infrastructure". The Committee called for the establishment of a public health agency in Canada, strategic investments in government public health science and the establishment of a permanent network, based in academia and the private sector, to broaden and deepen research response capacity in infectious diseases. The Committee suggested that the network established by the Consortium could become a model and evolve into a more permanent structure to address newly emerging infectious diseases in Canada.

Formation of the Canadian Rapid Research Response Team

The recent SARS outbreaks and concern regarding the potential for avian influenza to spread into human populations underscores the need for a permanent network that could evolve from the model established by the Consortium to rapidly mobilize Canada's health research community to address specific research questions posed by emerging pathogens. In response to this need, the CIHR-III, in consultation with Canada's health community, funding agencies and industry, has created the Canadian Rapid Research Response Team (C3RT). The mandate of the C3RT is to identify emerging health problems and assess if the problem may benefit from a rapid research response.

The C3RT is a standing steering committee with a primary interest in infectious disease research and is chaired by Dr. Singh, Scientific Director of CIHR-III. The team consists of scientific leaders drawn from a wide range of health research disciplines with the expertise to provide, on a rapid basis, recommendations and new knowledge about the research and products required to protect the health of the global population in the face of actual or potential emerging infectious diseases. To ensure that the appropriate expertise and knowledge is available, the Committee includes members representing multiple CIHR Institutes, Health Canada, the Canadian Food Inspection Agency, the Public Health Agency of Canada (PHAC), medical officers of health, infectious disease researchers, the private sector, provincial health ministries and international health agencies (Appendix 12).

Evaluation of the Relevance, Success and Efficiency of the CSRC

The aims of the evaluation, which was mandated by the Management Group, were to determine the Consortium's overall effectiveness, efficiency and relevance and to provide the Consortium with recommendations on how its performance could be improved. The evaluation focused on the Consortium's performance in three key coordination functions: establishment of research priorities for SARS, coordination of research funding among funding partners and alignment with international

activities, and facilitation of the integration of research findings. It will be used in the development of future structures such as the C3RT to coordinate research responses to new and emerging infectious diseases.

Dr. Natalie Kishchuk of Natalie Kishchuk Applied Research and Evaluation Inc. was contracted to carry out the evaluation. The evaluation report summarizes results relating to the key issues, highlights problem areas and includes recommendations for improvements. The stakeholder community widely agreed that many valuable lessons have been learned through the SARS experience and the CSRC experiment and that these should be applied in building an ongoing research response capacity for future emerging health threats. Key lessons learned were that the Canadian research community is willing and able to mobilize, to work in partnership and collaboration across sectors and institutions, and that there is a need to create a permanent national coordination entity to coordinate a rapid research response to emerging infectious diseases.

An executive summary of the evaluation report is presented in Appendix 13.

CONCLUDING REMARKS

In July 2003, human transmission of SARS was halted due to a massive public health effort. Fortunately, SARS has not reappeared, except for a few contained incidents in Asia, but it is likely that global outbreaks of new infectious diseases will continue in the future, particularly given globalization and intensive agricultural practices. Many scientists predict that the impact of SARS will be minor in comparison to the expected influenza pandemic or other, as yet unknown, infectious diseases. In many ways, the SARS outbreaks tested the ability of the Canadian research community and public health system to rapidly respond to an infectious disease crisis. The research community responded by forming the CSRC to identify research priorities and secure funding. Researchers funded by the CSRC made key discoveries that will protect the health of Canadians and help to treat SARS patients should SARS re-emerge. These researchers identified the cause of SARS, sequenced the SARS genome, developed sensitive assays to detect SARS in clinical samples, identified a potential therapy for SARS patients, determined which infected individuals had the best prognosis and developed candidate human SARS vaccines. The results of the research have been presented at numerous scientific conferences, published in several scientific journals and communicated to the public in hundreds of media interviews.

The National Advisory Committee on SARS and Public Health has called for the establishment of a public health agency in Canada, strategic investments in government public health science and the establishment of a permanent network, based in academia and the private sector, to broaden and deepen research response capacity in infectious diseases. The Canadian government, in response, has formed the PHAC. To establish a permanent network to identify emerging health problems and assess if the problem may benefit from a rapid research response, CIHR-III has created the C3RT, consisting of government health agencies, funding agencies, infectious disease researchers, international agencies and members of the private sector. The PHAC and the C3RT will greatly improve the public health and research response to future outbreaks of infectious diseases.

Appendices

APPENDIX 1:

PROFILES OF MANAGEMENT GROUP MEMBERS AND SPECIFIC CONTRIBUTIONS MADE TO THE CSRC

Canadian Institutes of Health Research (CIHR)

The Canadian Institutes of Health Research is the Government of Canada's agency for health research. Its objective is to excel, according to internationally accepted standards of scientific excellence, in the creation of new knowledge and its translation into improved health for Canadians, more effective health services and products and a strengthened Canadian health care system. At the onset of the SARS outbreaks in Canada, Dr. Alan Bernstein, President of CIHR, was instrumental in bringing together funding agencies and public and private sector organizations to form the Consortium and develop rapid research responses that address public needs. CIHR and its Institutes also provided funds in support of the SARS I "Host Response to Severe Acute Respiratory Syndrome" grants, SARS II "Public Health and Health Care System Preparedness and Response to SARS: Evaluations and Lessons Learned" grants and SARS III GlaxoSmithKline Small Molecule Pilot Project Grants Initiative.

CIHR Institute of Infection and Immunity: One of CIHR's 13 Institutes, the Institute of Infection and Immunity (CIHR-III) seeks to establish national leadership, priorities and programs that promote innovative research to reduce the global burden of infection and immune-based disease and improve quality of life. The CIHR-III made several key contributions to the CSRC. Dr. Bhagirath Singh, Scientific Director of the Institute, was instrumental in creating and leading the Consortium in his role as chair of the CSRC Management Group. Secretariat support for the Consortium activities was provided by Institute staff. The CIHR-III championed and provided funds in support of the rapidly launched SARS I "Host Response to Severe Acute Respiratory Syndrome" grants. The Institute also provided funds in support of SARS II "Public Health and Health Care System Preparedness and Response to SARS: Evaluations and Lessons Learned" grants, SARS III GlaxoSmithKline Small Molecule Pilot Project Grants Initiative and the SARS Patient Material Collection and Database Project.

CIHR Institute of Population and Public Health: One of CIHR's 13 Institutes, the Institute of Population and Public Health (CIHR-IPPH) supports research into the complex interactions that determine health, and its application to improve the health of individuals, communities and global populations. The CIHR-IPPH provided funds in support of the SARS II "Public Health and Health Care System Preparedness and Response to SARS: Evaluations and Lessons Learned" grants.

CIHR Institute of Health Services and Policy Research: One of CIHR's 13 Institutes, the Institute of Health Services and Policy Research (CIHR-IHSPR) is dedicated to supporting innovative research, capacity-building and knowledge translation initiatives designed to improve the way health care services are organized, regulated, managed, financed, paid for, used and delivered, in the interest of improving the health and quality of life of all Canadians. The CIHR-IHSPR provided funds in support of the SARS II "Public Health and Health Care System Preparedness and Response to SARS: Evaluations and Lessons Learned" grants.

CIHR Institute of Circulatory and Respiratory Health: One of CIHR's 13 Institutes, the Institute of Circulatory and Respiratory Health (CIHR-ICRH) supports research into causes, mechanisms, prevention, screening, diagnosis, treatment, support systems and palliation for a wide range of conditions associated with the heart, lung, brain (stroke), blood, blood vessels, critical care and sleep. The CIHR-ICRH provided funds in support of the SARS II "Public Health and Health Care System Preparedness and Response to SARS: Evaluations and Lessons Learned" grants.

Health Canada

Health Canada is the federal department responsible for helping Canadians maintain and improve their health. Health Canada undertakes a number of activities relative to infectious diseases such as SARS, including: surveillance, research, causes, control and public health and prevention. Together with other experts, Health Canada develops guidelines and recommendations for dealing with infectious diseases and investigates diseases of provincial or national importance. For SARS, a team of Health Canada professionals collaborated with partners to help to manage and control the disease.

Health Canada, specifically the team at the National Microbiology Laboratory and epidemiology and infection control staff, played a critical role in addressing the SARS crisis. Researchers worked quickly to determine the cause of SARS and to sequence, with scientists at the British Columbia Cancer Agency (BCCA) Genome Sciences Centre, the genome of the SARS virus. Health Canada also provided funds in support of the SARS I "Host Response to Severe Acute Respiratory Syndrome" grants and SARS II "Public Health and Health Care System Preparedness and Response to SARS: Evaluations and Lessons Learned" grants. Health Canada supported this research not only because of its commitment to improving the health of Canadians and promoting disease prevention, but because of a strong belief that this approach would have an impact in developing infection prevention measures and that the expected results will provide long-term benefits for Canadian and their neighbours around the world and reduce pressures on the health care system.

Ontario Research and Development Challenge Fund (ORDCF)

Created in 1997 by the Ontario government, the Ontario Research and Development Challenge Fund (ORDCF) promotes world-class research of interest to the private sector; encourages collaboration between the private sector and research institutions; attracts and retains top scientists and enables talented young scientists to pursue their research interests; and helps Ontario's research institutions build their R&D capacity, so they are able to obtain funding from other sources. Through the Challenge Fund, the province has committed more than $475 million to 113 research projects. In addition, private sector and research institution partners are investing more than $1.2 billion, bringing the total value of Challenge Fund-supported research projects to almost $1.7 billion. Given the impact of SARS on Ontario, and the role that Ontario companies might play in combating this and other infectious disease threats, the ORDCF was keen to support the CSRC and the research that it was coordinating. The ORDCF provided funds in support of the SARS I "Host Response to Severe Acute Respiratory Syndrome" grants.

Le fonds de recherche en santé du Québec (FRSQ)

The Fonds de recherche en santé du Québec (FRSQ) is a non-profit public body that reports to the Ministère de la Recherche, de la Science et de la Technologie (MRST). The FRSQ works in close collaboration with the Fonds québécois de la recherche sur la nature et les technologies and the Fonds québécois de la recherche sur la société et la culture. This synergy between the three funds is realized

through the work of the Comité permanent des présidents-directeurs généraux des fonds de recherche du Québec. FRSQ provided funds in support of the SARS I "Host Response to Severe Acute Respiratory Syndrome" grants.

Michael Smith Foundation for Health Research (MSFHR)

The Michael Smith Foundation for Health Research (MSFHR) was created by the Province of British Columbia to build BC's health research environment. In addition to being the province's premier funding agency for all types of health researchers, the Foundation plays a catalyst and leadership role, working across organizations and regions to increase BC's ability to advance and benefit from health research. The Government of British Columbia reinforced this provincial leadership role, charging the Foundation with financially managing and levering a $2.6 million seed investment announced by Premier Gordon Campbell to fast track the development of a SARS vaccine. Called SAVI (SARS Accelerated Vaccine Initiative), this national and international research effort is led by Scientific Director Dr. Brett Finlay (University of British Columbia) and Associate Director Dr. Robert Brunham (BC Centre for Disease Control). The Foundation is also providing funds to support the SARS Patient Material Collection and Database Project.

The Canadian Network for Vaccines and Immunotherapeutics (CANVAC)

The Canadian Network for Vaccines and Immunotherapeutics (CANVAC) is a unique network of 74 of the most highly recognized Canadian specialists in the fields of immunology, virology, and molecular biology, who are faculty members at 25 universities and affiliated research institutes. The Network scientists, in collaboration with 22 corporate partners, as well as interested government departments and agencies and several patient and consumer groups, are working towards the development of safe and effective vaccines for Canadians and people around the world against cancer and life-threatening viral infections, including those caused by HIV and the hepatitis C virus. CANVAC supported research within its own network and also provided funds in support of the SARS I "Host Response to Severe Acute Respiratory Syndrome" grants.

Protein Engineering Network of Centres of Excellence (PENCE)

Created in 1990 as part of the NCE (Networks of Centres of Excellence) program, the Protein Engineering Network of Centres of Excellence (PENCE) brings together more than 100 leading researchers from 20 Canadian universities and institutes. Comprising bioinformaticians, protein biochemists, physicists, chemists, cell biologists and engineers, its diverse expertise catalyzes profound science innovation, facilitates the creation of new technologies, and fosters the design of commercializable protein products and services. PENCE committed $300,000 towards a set of projects performed by researchers within its network aimed at fast tracking the development of therapeutics against SARS. This initiative was funded within six weeks of the announcement of the sequencing of the SARS genome.

The Mathematics of Information Technology and Complex Systems (MITACS)

Established in 1999, the Mathematics of Information Technology and Complex Systems (MITACS) is one of 20 federally funded Canadian Networks of Centres of Excellence (NCEs). MITACS research is centred about five key sectors of the economy: Biomedical and Health, Environment and Natural Resources, Information Processing, Risk and Finance, and Communication Networks and Security. The MITACS network involves 36 Canadian universities, 317 researchers, 455 trainees, and 145 partner organizations. Within the MITACS Biomedical and Health theme, epidemic modeling is an important focus. This is due to the global concern relating to communicable diseases where, most recently, SARS,

West Nile virus, BSE and avian flu have all caused widespread alarm. Epidemiological models are very important tools in dealing with these threats, since they lead to more informed public policy.

When the SARS crisis hit, MITACS formed a MITACS team of mathematicians, statisticians, virologists, epidemiologists and clinicians in partnership with Health Canada to develop models of the disease. In September 2003, MITACS, the Pacific Institute of Mathematical Studies (PIMS) and Health Canada held an international SARS conference at Banff International Research Station where Canadian researchers joined experts from the U.S. Center for Disease Control, Britain, Australia and Taiwan to map a future strategic plan for research. In June 2004, MITACS, the Mathematical Sciences Research Institute (MSRI) and PIMS sponsored a special program on Mathematical Modeling of Infectious Diseases, consisting of an International Summer School and a Workshop. MITACS also funded research projects within its network.

GlaxoSmithKline

GlaxoSmithKline, one of the world's leading research-based pharmaceutical and healthcare companies, is committed to improving the quality of human life by enabling people to do more, feel better and live longer. In Canada, GlaxoSmithKline employs approximately 1,800 people and is a top-25 investor in Canadian research and development, contributing more than $100 million annually. The company is also one of the top 10 corporate charitable donors, investing more than $7.5 million annually, and is recognized as one of the 50 best companies to work for in Canada. GlaxoSmithKline provided funds in support of the SARS III GlaxoSmithKline Small Molecule Pilot Project Grants Initiative launched by the CIHR Institute of Infection and Immunity and the CIHR/Rx&D Research Program.

Sanofi Pasteur Limited

In Canada, Sanofi Pasteur Limited is the country's premier vaccine company, manufacturing or distributing 30 vaccines and immunotherapeutic products, which protect against 17 infectious diseases and common illnesses. For nearly 90 years, Sanofi Pasteur Limited has protected Canadian against preventable diseases. Sanofi Pasteur Limited is providing funds in support of the SARS Patient Material Collection and Database Project.

Canadian Lung Association

The mission of The Lung Association is to lead national and international lung health initiatives in preventing lung disease, helping people manage lung disease and promoting lung health. A unique partnership of ten provincial Lung Associations from coast to coast, the Canadian Lung Association acts to strengthen the work of the provincial associations through support of research, advocacy for improved respiratory health, communications and coordination of services. One of the roles of the Association is to provide accurate and credible information to the public in response to emerging issues in lung health such as SARS. The Canadian Lung Association in conjunction with L'Association Pulmonaire du Québec, provided funds in support of the SARS II "Public Health and Health Care System Preparedness and Response to SARS: Evaluations and Lessons Learned" grants.

APPENDIX 2:

SUMMARY OF THE RESEARCH PERFORMED BY THE SARS I FUNDED RESEARCH TEAMS

Towards an understanding of severe acute respiratory syndrome: The Canadian SARS Research Network

Principal Investigator/Team Leader: Dr. Mark Loeb, McMaster University
Project leaders:

Dr. David Earn, Department of Mathematics and Statistics, McMaster University
Dr. David Kelvin, Experimental Therapeutics, Toronto General Research Institute, University Health Network
Dr. Gary Levy, Multi Organ Transplant Program, Toronto General Hospital, University Health Network
Dr. Donald Low, Department of Microbiology, Mount Sinai Hospital
Dr. Marie Louie, Department of Microbiology, Sunnybrook & Women's College Health Sciences Centre
Dr. Allison McGeer, Department of Microbiology, Mount Sinai Hospital
Dr. Susan Richardson, Division of Microbiology, The Hospital for Sick Children

Diagnostics Theme

The broad objectives of the diagnostic group include the development and optimization of diagnostic tests for SARS-CoV and also the study of the genetic variability of the virus during the course of the Toronto outbreak. Studies have revealed that extraction methodologies are key to enhancing sensitivity. Extraction and PCR methods that produce the highest sensitivity of detection were determined. The sensitivity and specificity at different clinical time points is currently being evaluated. For the serological assay, the team examined the specificity of 12 different assays in 6 laboratories using 32 sera samples. Studies are now under way to determine the relative sensitivity and specificity of the best assays using 300 to 500 sera from SARS patients, controls, and patients with atypical pneumonia from pre-SARS era. This research will establish diagnostic standards that will be critical to the detection and containment of SARS in future occurrences of this disease locally and worldwide. The research results have been and will continue to be disseminated at national and international medical conferences. Work on the last objective (genetic variability) is just underway. Work from this collaborative group is leading to further funding initiatives that are focused on enhancing the diagnosis of respiratory infections overall. A pilot project undertaken by members of the group has shown that in outbreaks of respiratory infection, an etiologic diagnosis is made in only about 50% of the cases. Work is underway using the expertise acquired in the present study to achieve enhanced (i.e. molecular) detection of influenza and other respiratory viruses, such as non-SARS human coronaviruses, respiratory syncytial virus, human metapneumovirus, parainfluenza viruses and rhinoviruses, in addition to bacterial agents of pneumonia such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. The ability to make a rapid, reliable diagnosis of the cause of respiratory infections in close to 100% of cases will afford significant benefits with respect to infection control, patient management, treatment and outcome.

Clinical Theme

Objectives: 1) To describe the clinical course of patients diagnosed with probable and suspect SARS, 2) To determine predictors of illness severity and disease outcome, 3) To assess the efficacy of systemic steroids and/or ribavirin in the treatment of SARS, 4) To identify prognostic factors that predict clinical outcome in SARS, 5) To distinguish between clinical symptoms and laboratory abnormalities due to SARS from those due to therapy with ribavirin, 6) To determine the incidence of adverse drug effects due to therapy with ribavirin. The following components of the clinical study were designed to address the objectives outlined above: 1. Retrospective Cohort Study, 2. Long-term Pulmonary, Functional and Quality of Life Outcomes Study Psychological Impact of SARS Study, 3. Mortality Cohort Study, 4. Radiology Study, 5. Pathology Study. To date 351 charts have been abstracted and 9 charts remain to be completed. Thirty-six charts were randomly selected for duplicate abstraction, and 29 abstractions have been done. Duplicate data entry has been completed on all available charts. Statistical analysis is underway and limited preliminary results are available. The SARS follow-up clinic began on July 11, 2003 and continues to follow approximately 120 patients. To our knowledge, this represents the largest follow-up study after SARS.

Epidemiology Theme

The objectives of the epidemiologic section were to determine risk factors for SARS in health care workers, and to identify the extent of subclinical illness in exposed health care workers. This proposal provided funding for two parallel cohort studies of risk in intensive care unit staff exposed to patients early in the outbreak at the Scarborough Grace Hospital and the Mount Sinai Hospital and for the development and implementation of a cohort study to identify sub-clinical infection in 1350 health care workers. The cohort studies identified exposure in the patient's room, proximity to airway, and lack of personal protective equipment (particularly masks) as risk factors for infection. There was suggestive data that N95 as opposed to surgical masks, might be more protective. The seroprevalence study in health care workers identified that the incidence of asymptomatic infection is low, estimated at 10% or less of the symptomatic infection rate. These data have been presented in abstract form, and a manuscript is in preparation. The data have been presented at Health Canada meetings, to the Walker Commission and the Ontario Task Infection Control Guidelines Task Force, and used by these groups and the US Centers for Disease Control and Prevention in the development of recommendations for infection control in hospitals. Plans are in place to share the data with staff of the affected hospitals, and to present the data at a meeting on Global Health and Infection Prevention in Toronto in the fall of 2004. The CIHR funding was used to leverage grant funding from the Ontario Ministry of Health and Health Canada to expand these studies to examine the risks of infection in health care workers despite the use of precautions, to study exposure risk in the emergency department at the Scarborough Grace Hospital early in the epidemic, and to complete the investigation of transmission and risk factors for transmission in units other than the intensive care unit at the Scarborough Grace Hospital.

Modeling Theme:

The modeling group has focused on developing methods to evaluate the capacity of cities to withstand a resurgence of SARS, or emergence of a similar pathogen. It should be noted that one of the key goals outlined in our original grant proposal was to build a model that could successfully capture the dynamics within Toronto. This has been impossible because the line-listed case data required has never been made available to us, despite numerous promises from several potential sources.

SARS: A scientific collaborative to support public health response through vaccination

(Note: Some of this work was a joint effort with the SARS Accelerated Vaccine Initiative, outlined in Appendix 3)

Principal Investigator/Team Leader: Dr. Danuta Skowronski, University of British Columbia
Co-Principal Applicants:
Dr. Lorne Babiuk, University of Saskatchewan
Dr. Timothy Booth, University of Manitoba
Dr. Robert Brunham, University of British Columbia
Dr. Marco Marra, University of British Columbia
Dr. Martin Petric, University of British Columbia
Dr. Babak Pourbohloul, University of British Columbia
Dr. David Scheifele, University of British Columbia

- Development and validation of diagnostic tests including PCR and serologic neutralization assays that have been applied to more than 400 specimens and shared with other national and international agencies. Applied serially to probable cases, these tests have evaluated the kinetics of the humoral immune response to SARS. Applied in combination and with other molecular techniques, investigators have used these tests to effectively rule out SARS in highly publicized scenarios of possible SARS re-emergence (*i.e.* the outbreak in a long term care facility in Surrey, British Columbia in August 2003). Presentation at numerous conferences and a manuscript related to practical application in facility outbreak has been submitted.

- Sero-epidemiologic surveys completed amongst household and health care contacts (~450) of confirmed cases of SARS in British Columbia. The purpose of surveys was to assess the extent and distribution of spread of SARS in the only Canadian province other than Ontario to receive multiple importations of the disease in spring, 2003. This survey confirmed successful containment of SARS in British Columbia limited to four importations and one laboratory-confirmed secondary case with no further household, nosocomial or community transmission identified by application of retrospective serologic test methods. A manuscript comparing the different experience with SARS in Vancouver compared to Toronto on epidemiologic factors (agent/host/environment) has been completed and submitted for publication.

- Development of a mathematical model to predict the spread of SARS through communities at various geographic scales and for quantitatively comparing the impact of various public health interventions including contact and/or transmission reducing strategies or immunization. Computer simulations employing contact network theory help explain the difference in SARS experiences between Toronto and Vancouver by accounting for multi-factorial influences.

- Animal models for disease and vaccine experiments were identified. In experiments, mice, and to a lesser extent, chickens, had evidence of viral sequences after infection but neither became ill. Ferrets demonstrated infection as well as some pathology in the lungs, but had no evidence of clinical disease.

- Development of an inactivated whole SARS virus vaccine formulated in alum. The virus is inactivated with beta-propriolactone by a process that maintains high levels of biologically active spike (S) protein.

- Testing of the inactivated whole SARS virus vaccine in mice and in ferrets.

- Testing immunogenicity of different vaccine preparations in mice using different adjuvants (alum versus polyphosphazene) to assess type and strength of immune response induced.

- Further collaborations by co-investigators has led to development of adenovirus vector vaccine expressing S, nucleocapsid (N) or a combination of S and N proteins to induce protection as well as a DNA vaccine based on plasmid expressing S gene.

- Combinations of DNA vaccine and S protein or inactivated whole SARS virus vaccine have been evaluated in mice to assess strength and type of immune response and the immune modulator functions and synergistic effects of polyphosphazene with or without CpG.

- Peptides comprising four sequences predicted to be highly immunogenic were synthesized and used to prepare rabbit antisera for future studies to detect S protein production by recombinant means. Independently, a collaborator (Dr. P. McGeer) screened convalescent sera and showed strong antibody response to three of the four synthesized peptides. These sera have been invaluable for detecting expression of S protein and have been shared with other national and international agencies to detect expression of S protein in baculovirus, adenovirus and by DNA plasmids.

- The team is also embarking on *in vitro* evaluation of the immunologic correlates (humoral and cytokine responses) of disease and severity among persons with SARS and matched controls in the Toronto area. Progress on this domain was delayed because of initial inability to access patients with SARS in the Toronto area that has now been resolved.

Molecular markers of immunity and outcome for SARS

Principal Investigator/Team Leader: Dr. James Dennis, Samuel Lunenfeld Research Institute, Toronto
Co-Investigators:
Dr. Eleanor Fish, Division of Cell & Molecular Biology, Toronto General Research Institute, University Health Network
Dr. Chi-Yip Ho, Samuel Lunenfeld Research Institute, Mount Sinai Hospital
Dr. Katherine Siminovitch, Samuel Lunenfeld Research Institute, Mount Sinai Hospital

- A major accomplishment lead by Dr. Fish was the clinical trial of SARS patients treated with interferon (alfacon-1). The treatment was efficacious and safe, and the findings have been reported in JAMA. The WHO/CDS/CSR have examined the team's interferon protocols and the results, and will consider using this treatment in future outbreak of SARS or severe influenza. This is all the more remarkable considering that interferon has been available for years, and the study using this new consensus form of interferon is one of the first to show efficacy in a setting of acute viral infection.

- Serum cytokines and virus in the same cohort of interferon treated and non-treated control patients have been analysed. This work has revealed different patterns of cytokines, and although the number of patients is small it can be concluded that there is considerable heterogeneity in the population for responses to infection. This re-enforces the proposal that better information is needed on the molecular profiles that define effective and ineffective host immune responses to viral infection.

- An improved method for re-sequencing SARS CoV using microarry methods and Affymetrix re-sequencing chips commissioned by NIH was developed. Sequence changes in the virus between different patients and in various tissue of the same patient are currently being tracked to observe the changes that may occur with the natural history of the disease. In collaboration with Dr. Kevin Kain, more than 100 samples have been sequenced and analysed.

- The team developed a novel pre-treatment method for RT-PCR to eliminate contaminating DNA when RT-PCR amplifying RNA viruses. A patent application will be filed and a methods paper is being drafted.

- The team developed methods for detection of the transducer of interferon signaling, the STAT1α and STAT3α proteins, by mass spectrometry. It has been difficult to detect the β form by mass spectrometry, and the team is continuing to refine these methods with assistance from Dr. Ashman from MDS Sciex. The company is interested in diagnostic uses for mass spectrometry.

- Studies on the mouse coronavirus MHV-3 have demonstrated utility as a model of host susceptibility, and studies are planned to identify strain-specific gene alleles that influence outcome to MHV-3 infection.

- DNA samples from patients and immediate family members are being assembled for SNP genotyping to analyze DNA. This process has been hampered by poor coordination of repositories and databases for this material in the aftermath of SARS. The DNA will be carefully archived and a resource for future studies on genes and severity of disease.

The team submitted a proposal to the last CIHR competition to complete the SARS research program. The identification of host determinants that dictate disease severity will require a continued effort with multiple approaches. Re-sequencing will be expanded to include other virus such as influenza and West Nile. Re-sequencing is fast and accurate, and this technique should be used to study the evolution of viruses during the course of outbreaks. The information could be used to discover changes in the virus that affect host resistance.

The development of a rapid multiplex SARS assay

Principal Investigator/Team Leader: Dr. Michel Bergeron, Centre hospitalier de l'Université Laval
Co-Investigator: Dr. Guy Boivin, Centre hospitalier de l'Université Laval

The team has developed rapid and reliable RT-PCR assays for the detection of all four coronaviruses known to infect humans. The team originally proposed to detect, SARS-HCoV, HCoV-OC43 and HCoV-229E, but in the spring of 2004 added the recently discovered Coronavirus from the Netherlands, HCoV-NL. The assays for these four respiratory viruses are a valuable addition to the panels of respiratory viruses assays already developed in the lab (Influenza A and B, hRSV, hMPV, Parainfluenza 1 and 3, Adenovirus, Rhinovirus and Enterovirus). Therefore, 13 different respiratory viruses can now be detected directly from clinical samples. This permitted the identification of HCoV-NL in nasopharyngal aspirates from Canadian children and will allow for a study of the prevalence of all important respiratory viruses in this population.

In addition, a very rapid and simple sample preparation procedure for extracting viral nucleic acids from respiratory specimens is in development. This procedure has potential for automation and significant cost reduction.

The SARS-CoV assays were validated using purified target RNA, however, the unavailability of clinical specimens from SARS patients hampered further progress for assay refinement. The team participated in two proficiency panels submitted respectively by the National Microbiology Lab (NML) and the Ontario Provincial Lab. The SARS-HCoV assay detected all positive samples submitted by the NML but missed some of the Ontario samples containing the lowest viral titers. There were no false negatives with the assays. The apparent lack of sensitivity with the Ontario panel could be explained by the fact that only respiratory samples were used during the development of the tests, while the Ontario specimens were spiked with fecal matter, a specimen type for which a sample preparation procedure had not been optimized.

Knowledge gained during this project was pivotal in obtaining part of a $12.6 million Genome Canada grant. The findings will be used to create automated analysis systems using microarrays for the detection of the most important human respiratory viruses.

APPENDIX 3:

SUMMARY OF THE RESEARCH PERFORMED BY THE SARS ACCELERATED VACCINE INITIATIVE (SAVI) RESEARCH TEAM

SARS Accelerated Vaccine Initiative

Co-Principal Investigators: Dr. Brett Finlay, Scientific Director, SARS Accelerated Vaccine Initiative (SAVI) and Dr. Robert Brunham, Associate Director, SARS Accelerated Vaccine Initiative (SAVI)
Co-Investigators:

Dr. Samuel Abraham, BC Cancer Agency
Dr. Caroline Astell, BC Cancer Agency's Genome Sciences Centre
Dr. Lorne Babiuk, Veterinary Infectious Disease Organization (VIDO), University of Saskatchewan
Dr. David Patrick, UBC Centre for Disease Control
Dr. Martin Petric, BC Centre for Disease Control
Dr. Michael Rekart, BC Centre for Disease Control
Dr. Kris Roberts, SAVI Project Coordinator
Dr. Rachel Roper, SAVI Program Director – Biologicals
Dr. Raymond See, SAVI Program Director – Vaccine Development
Dr. Danuta Skowronski, BC Centre for Disease Control
Dr. David Scheifele, Vaccine Evaluation Centre, B.C.'s Children's Hospital
Dr. Aubrey Tingle, Michael Smith Foundation for Health Research

SARS Accelerated Vaccine Initiative (SAVI) is a BC-led international research initiative, launched with $2.6 million from the BC provincial government, to fast-track the development of a human vaccine for SARS. The goals are two-fold:

- Develop an effective SARS vaccine as quickly as possible
- Develop a new model for scientific collaboration to more effectively address emerging public health needs

Developing a new vaccine usually takes years but by adopting an emergency-management model, which involves following a highly focused and coordinated program and conducting activities concurrently, rather than sequentially, the objective is to have a vaccine in human trials in a year.

SAVI researchers decided to pursue three vaccine candidate strategies in parallel given the potential seriousness of a SARS outbreak and the wide acknowledgement that a vaccine is the best hope for eliminating the medical and economic threat of SARS. Within 6 months, SAVI has developed three vaccine candidates. Two of the vaccine candidates (whole killed virus vaccine, prepared at the BC Centre for Disease Control, and adenovirus vector containing two SARS genes from McMaster University) have been tested in head-to-head studies in two independent SARS animal models developed by the Southern Research Institute, Alabama. Results show that in both a mouse and ferret model for SARS, the whole-killed virus vaccine induced neutralizing antibodies, markedly reduced viral titers in the lungs as well as significantly decreased gross pathology. Histopathological analysis of the lung tissues is still ongoing. Similarly, a combination of adenoviruses containing two SARS genes also significantly reduced viral titers

in the lungs in both animal models. Within 14 months from the start of vaccine development, SAVI has developed two SARS vaccines that show proof-of-principle in animal models. Two other SARS vaccines, a recombinant spike protein and a modified vaccinia virus are also close to being tested in animal trials. Therefore, SAVI will have four different SARS vaccine candidates by the end of 1.5 years that will have completed pre-clinical trials.

Although the number of cases of SARS in 2004 is low, these vaccines will be mobilized quickly into human clinical trials should a major outbreak of the disease occur. It is expected that the vaccine will have major benefits for high risk individuals, such as health care workers, airline employees, and individuals at risk due to exposure to infected patients.

The rapid research response mechanisms, such as those used by SAVI, have shown that the application of emergency management techniques, together with rapid response research can be highly effective when applied appropriately to new infectious diseases.

APPENDIX 4:

SUMMARY OF THE SARS RESEARCH PERFORMED BY CANVAC

Principal Investigators:

Dr. David Kelvin, Toronto General Research Institute
Dr. Jack Gauldie, Pathology and Molecular Medicine, McMaster University
Dr. Grant McFadden, BioTherapeutics Research Group, Robarts Research Institute
Dr. Gregory Dekaban, BioTherapeutics Research Group, Robarts Research Institute
Dr. Heinz Feldman, Health Canada
Dr. Rafick-Pierre Sékaly, Centre de recherche du Centre hospitalier de l'Université de Montréal, McGill University
Dr. Michel Klein, CANVAC

Research summary

The strategic plan for the CANVAC SARS research team was to first acquire maximal immunological information on SARS infected persons and then use this information in the creation of SARS vaccines that could be applied clinically. The program used robust genomic and targeted proteomic methodologies to acquire correlates of immune protection and then used strategic partnerships with corporate vaccine developers to create SARS vaccines for clinical utility.

Progress on understanding the host response to acute SARS infection:

- Using cytometric bead arrays for assaying cytokine and chemokine profiles the team was able to identify that the chemokine, IP-10, is a signature of SARS illness at the earliest stages of infection.
- Using cDNA micro-arrays, the team determined that all patients regardless of outcome elicit a robust interferon response. Furthermore, a specific defect in the transition to adaptive immunity was observed in patients that have a severe course of illness.
- Animal models of SARS infection indicates that the virus attacks the lymphoid compartment.

Correlates of Protection:

- Using functional epitope mapping, 11 T cell epitopes that elicit functional T cell responses against the SARS N protein were identified. This protein is likely critical for mounting T cell immunity.
- Using the Iopia screening strategy in collaboration with Beckman Coulter, 43 T cell epitopes across 8 different MHC class I alleles were identified. Four tetramers were generated that can be used as a highly sensitive assay for patients infected with the SARS coronavirus.

Vaccine Development:

- Three different vector systems have been employed to create SARS vaccine vectors. A codon optimized spike gene plus the N gene of the Tor2 strain of SARS have been inserted into a single Adenovector. Immunogenicity indicates this construct is superior to first generation constructs. Optimized spike and N have been placed into the vaccine measles strain in collaboration with Berne Biotech. These two vectors are currently in challenge studies. A third pox vector, MVA, is currently under construction with the spike and N genes.

The corporate collaborators for these projects were BD Biosciences, Beckman Coulter, Berne Biotech and TransGene.

APPENDIX 5:

SUMMARY OF THE SARS RESEARCH PERFORMED BY PENCE

PENCE SARS 1: High-Throughput Cloning and Expression of SARS Proteins

Principal Investigator/Team Leader: Dr. Cheryl Arrowsmith , Clinical Genomics Centre, Ontario Cancer Institute, University of Toronto
Co-Investigators:
Dr. Aled Edwards, Clinical Genomics Centre, Banting and Best Institute, University of Toronto
Dr. Lawrence McIntosh, University of British Columbia

The purpose of this project was for one central laboratory to clone the genes encoding as many SARS-CoV proteins as possible into two convenient plasmid systems that will be freely available to all interested researchers. These clones are the necessary first step towards most biochemical and biophysical studies of the viral proteins. The advantages of this approach are multi-fold: (i) This is a systematic, "whole proteome" effort that will help to determine if each putative gene product indeed corresponds to a defined protein, amenable to purification and detailed biochemical and biophysical analyses. (ii) The Arrowsmith/Edwards group have the established infrastructure and personnel to carry out high-throughput cloning in a rapid and cost efficient manner, as required for structural proteomic studies. (iii) This will avoid duplication of effort by individual researchers, while providing the entire community with co-ordinated access to standard expression vectors for many SARS-CoV proteins.

Under the supervision of Dr. Savchenko (Structural Proteomics Group Leader), these will be cloned into two systems: the pET15b *E. coli* expression vector to produce proteins with an N-terminal His-tag, cleavable with TEV protease, and the entry vector of the Gateway system, allowing for facile transfer by *in vitro* recombination into a number of prokaryotic and eukaryotic expression vectors. In parallel with DNA sequencing, the pET15b clones will be tested for the expression, solubility, and reversible refolding of the encoded protein. This project will involve a systematic first pass effort to clone the currently predicted SARS-CoV proteins. All of the results of this work will be posted on the UVic-PENCE SARS website (following the model of the Clinical Genomics Centre http://www.uhnres.utoronto.ca/proteomics/), and the clones will be freely available to researchers interested in pursuing further studies.

PENCE SARS 2: The 3CL Protease of the SARS Coronavirus: a SARS Target

Principal Investigator/Team Leader: Dr. Lindsay D. Eltis, Department of Microbiology and Immunology, University of British Columbia
Co-investigators:
Dr. Eric Brown, Department of Biochemistry, McMaster University
Dr. Michael N.G. James, Department of Biochemistry, University of Alberta
Dr. John C. Vederas, Department of Chemistry, University of Alberta
Dr. David S. Wishart, Department of Computing Science and Biological Sciences, University of Alberta

The 3C-like protease ($3CL^{pro}$), is predicted to be essential to the life cycle of SCV and is therefore an important target for novel drugs to treat SARS. Through a multidisciplinary, highly collaborative effort, $3CL^{pro}$ was overexpressed and purified, and an assay to detect its activity was developed. Strong, reversible inhibitors of the protease were obtained through two independent approaches: a) synthesis, and b) high throughput screening of a small molecule library. These inhibitors are lead compounds in the development of novel SARS drugs. Ongoing research involves: engineering $3CL^{pro}$ to facilitate its steady-state kinetic characterization; understanding the mode of binding of the lead compounds; modifying the structures of these compounds to improve inhibition and their likely bioavailability; and designing new motifs as potent, reversible inhibitors. The remainder of the hits in the Maybridge library that could not be studied on the first pass will also be evaluated. The substrate specificity of SCV-$3CL^{pro}$ will be investigated using a biological selection developed for $3C^{pro}$. Finally, the covalent inhibitors of $3CL^{pro}$ will be modified to develop a reagent for proteomic analyses of the SCV replicase complex.

As part of this PENCE grant, SCV-$3CL^{pro}$ was expressed as a fusion protein with a cleavable his-tag (ht-$3CL^{pro}$) using a T7-based system in *E. coli*. Tagged and non-tagged $3CL^{pro}$ had essentially identical specific activities (FRET-based assay, *vide infra*). Purified $3CL^{pro}$ eluted as two peaks from the gel filtration column, apparently corresponding to monomeric and dimeric forms. The K_d between the subunits is ~0.1 mM. Importantly, only the dimer appears to be catalytically active.

A continuous assay for $3CL^{pro}$ proteolytic activity was developed based on fluorescent resonance energy transfer (FRET). A peptide was synthesized using anthranilate and nitrotyrosine (Abz-SVTLQSG-Tyr(NO_2)R) and was used to characterize SCV-$3CL^{pro}$ and its inhibitors. This is the first developed continuous assay of SCV-$3CL^{pro}$ activity. A pNA-based peptide substrate was synthesized for a colourimetric assay, but was not detectably cleaved.

A major objective of this PENCE grant was to develop inhibitors of SCV-$3CL^{pro}$ to be used as lead compounds and drugs for the treatment of SARS. Due to their similarities in mechanism and active site architecture, it was hypothesized that $3CL^{pro}$ and $3C^{pro}$ may be susceptible to inhibition by the same classes of compounds. Accordingly, $3CL^{pro}$ was tested with many of the laboratory's previously-synthesized inhibitors of hepatitis A (HAV) and human rhinovirus-14 (HRV14) $3C^{pro}$'s. In addition, several dozen variants of structures 1 and 2 were synthesized and tested. Inhibitors of SCV-$3CL^{pro}$ were also obtained via high throughput screening (HTS) against a small molecule library of 50,000 compounds sourced from Maybridge plc. Six compounds and substrate analog 3 are the lead compounds. They are being further modified, and will be examined using molecular modeling, x-ray crystallography and NMR. NMR spectra of sufficient quality have yet to be obtained.

The overall objectives of the next phase of the research are: a) to further understanding of SCV-$3CL^{pro}$; and b) to improve the lead compounds. To help achieve these objectives, $3CL^{pro}$ will be engineered to stabilize the dimer. This should facilitate its steady-state kinetic characterization, including inhibitor studies. Improving inhibitors of SCV-$3CL^{pro}$ will focus on understanding the mode of binding of the 7 lead compounds, modifying the structures of these compounds to improve inhibition and their likely bioavailability, and designing new β-amino ketone motifs as potent, reversible inhibitors. In addition, the remainder of the hits in the Maybridge library that were not selected in the first round of secondary screening will be evaluated. Finally, the substrate specificity of SCV-$3CL^{pro}$ will be investigated using a biological selection developed for $3C^{pro}$, and covalent inhibitors of $3CL^{pro}$ will be modified to develop reagents for proteomic analysis of the replicase complex.

PENCE SARS 3: Development and Application of Peptide Arrays and FRET Imaging Microscopy for Identifying and Evaluating SARS-Coronavirus 3CL Protease Inhibitors in Live Cells

Principal Investigator/Team Leader: Dr. François Jean, Department of Microbiology & Immunology, University of British Columbia
Co-investigator: Dr. Peter van Dijken, Pepscan Systems, The Netherlands

The main objective of this initial PENCE funding was to develop a robust and efficient system to express the SARS-CoV $3CL^{pro}$ in mammalian cells in order to i) facilitate its enzymatic characterization and ii) allow the screening of possible inhibitory compounds in a physiologically relevant environment. $3CL^{pro}$ was successfully cloned and a recombinant adenovirus encoding $3CL^{pro}$ was generated. The protease activity of Ad-$3CL^{pro}$ expressed in mammalian cells will be demonstrated using a continuous assay utilizing our novel library of SARS-CoV internally quenched fluorogenic substrates (IQFSs).

The current major objective is to complete the development and optimization of a novel FRET cell-based assay in order to identify and evaluate putative $3CL^{pro}$ inhibitors in live cells. The first aim is to thoroughly characterize the intrinsic proteolytic specificity ("proteolytic fingerprint") of recombinant purified $3CL^{pro}$ using peptide arrays consisting of IQFSs derived from the 12 putative SARS-CoV $3CL^{pro}$-dependent polyprotein cleavage sites. The peptide arrays will be designed and prepared in collaboration with Pepscan Systems (Dr. Peter van Dijknen, The Netherlands). The second aim is to prepare constructs expressing GFP-FRET substrates to enable the detection of $3CL^{pro}$ endoproteolytic activity in live cells. The GFP-FRET substrates will consist of two GFP variants joined by a linker region corresponding to optimal $3CL^{pro}$ cleavage sequences and will be prepared based on the results of the kinetic studies performed with the peptide arrays. GFP-FRET substrates will be transfected into cells already infected with recombinant adenovirus expressing SARS-CoV $3CL^{pro}$ (Ad-$3CL^{pro}$) and cleavage of the substrates will be monitored by live FRET microscopy using a Discovery-1 imaging system (Universal Imaging). The third aim is to apply the FRET cell-based assay to the rapid and effective screening of small molecule compound libraries to identify potential inhibitors of SARS-CoV $3CL^{pro}$. Naturally-occurring marine compound libraries will be used for this purpose in collaboration with Dr. R. Andersen (UBC). With the increased incidence of emerging viruses worldwide, the proposed combination of peptide arrays and live cell FRET microscopy represents a potentially widely applicable approach for the rapid proteolytic "fingerprinting" of novel virally encoded proteases and a robust method for high-throughput live cell protease assays for drug discovery.

PENCE SARS 4: Large-Scale Production of the Spike Protein of SARS-CoV for Biochemical, Immunological and Structural Studies

Principal Investigator/Team Leader: Dr. James Rini, University of Toronto
Co-investigator: Dr. Alan Cochrane, University of Toronto

The complete sequence of the SARS-CoV reveals that, unlike some members of the family, SARS-CoV does not possess a hemagglutin-esterase protein. As such, host cell recognition and binding is almost certainly mediated solely through the spike glycoprotein (S). Moreover, the protein is likely to represent the dominant SARS-CoV immunogen. The goal of this study was to implement methods to express large amounts of soluble forms of the S protein in a bioreactor-based mammalian expression system for biochemical, immunological and structural studies aimed at the development of antiviral therapeutics.

To characterize the coronavirus S-protein cDNAs of spike proteins were obtained from three human coronaviruses, SARS-CoV, hCoV-229E, hCoV-OC43 as well as that from mouse hepatitus virus (MHV). In addition, cDNAs of angiotensin converting enzyme 2 (ACE2) aminopeptidase N (APN), and mCEACAM1, the cell surface receptors of SARS-CoV, hCoV-229E and MHV, respectively, were obtained. Expression of the following has been demonstrated: i) three soluble fragments of the SARS-CoV S-protein containing the ACE2 binding site, ii) two soluble fragments of ACE2, and iii) the entire ectodomains of the S-proteins of hCoV-229E and hCoV-OC43. Stable cell lines expressing each of these fragments are being generated. In addition, the vectors are also being used to generate cell lines producing smaller soluble fragments of the hCoV-229E S-protein and APN, its cell surface receptor.

The production of large amounts of S protein and various S protein fragments will immediately facilitate binding studies aimed at defining its interactions with host cells. The role played by carbohydrate-binding is of particular interest as carbohydrate-based inhibitors have been successfully used as anti-influenza agents. The S protein is the main immunogen of SARS-CoV and the ability to produce various protein fragments will also aid in the development of subunit vaccines, an approach already successfully used against BCoV. In the long term the aim is to determine the x-ray crystal structures of relevant domains and/or receptor complexes (*e.g.* sialic acid or larger protein/glycoprotein host cell complexes) to understand the mechanisms underlying virus binding and entry.

In the course of this work, collaborations were established with Drs. Nabil Seidah (Montreal), Pierre Talbot (Laval) and David Kelvin (Toronto). It is anticipated that the potential for commercialization on this project is relatively high.

PENCE SARS 5: Implication of the Proprotein Convertases in the Processing and Infectivity of SARS-CoV

Principal Investigator/Team Leader: Dr. Nabil Seidah, Institut de Recherches Cliniques de Montréal
Co-investigators:
Dr. Emil Pai, University of Toronto
Dr. Robert Ménard, Biotechnology Research Institute

In many infectious viruses the surface glycoprotein is processed by one or more member(s) of the proprotein convertase family, resulting in an enhancement of the fusiogenic properties of the virus and hence of its infectivity. Based on the sequence in the Web (Acc# NP_828851), it was predicted that in the infectious particle the SARS spike S-glycoprotein would be processed by an as yet unidentified host cell enzyme particularly abundant in lungs, as this is the first tissue in contact with the aerosol-spread viral particles. The cDNA for full length S-glycoprotein that will have a V5-tag at its C-terminus for immunological detection has been ligated into a pIRES2-EGFP bicistronic expression vector. CHO-FD11 (Furin-negative) cells stably expressing individually each of the proprotein convertases Furin, PC5A, PC5B, PC7 and PACE4 were generated and showed that each transfectant resulted in 100% processing of a model precursor proPDGF-A into PDGF-A. ProSgp appeared as a mixture of an endoplasmic reticulum form (endoH sensitive; ~220 kDa) and a ~250 kDa Golgi-associated form (endoH insensitive). A small amount of non-glycosylated proSgp was also detected (~160 kDa). The data suggest that in these cells, the ~220-250 kDa proSgp is processed at three sites. The first one generated a ~220 kDa product and the second an ~80 kDa product, both of which are enhanced by overexpression of either of the membrane-bound convertases Furin or PC7, but not by the soluble enzymes PC5A or PACE4. A third ~110 kDa product does not seem to be generated by the convertases. Transient transfections of CHO FD11 cells

confirmed these data and further showed that SKI-1 or NARC-1 are not involved in the processing of proSgp. The importance of the transmembrane-cytotolic tail at the C-terminus of Furin was confirmed by co-expression of either full-length furin or its C-terminally truncated versions BTMD-furin and BCRD-furin. Further, the Furin-generated ~220 kDa product through processing of proSgp at its N-terminus was shown to be inhibited by the proprotein convertase inhibitor dec-RVKR-CMK. Thus, Furin-like convertases cleave proSgp first at the N- terminus (~220 kDa product) and later on in the middle to generate the ~80 kDa S2 subunit.

Since the SARS-CoV is known to infect Vero cells, the laboratory tested whether the inhibitor dec-RVKR-CMK could interfere with the viral infectivity or pathogenic effects. The PC-inhibitor dec-RVKR-CMK was shown to abrogate the CPE caused during SARS infection and this effect is due to the lack of S1 and S2 processing. Finally, work has begun on the recently identified Sgp receptor, namely human angiotensin converting enzyme 2 (ACE2). To date, it has been shown that while the basic aa-specific convertases do not cleave ACE2, it is still processed by an as yet unknown cellular protease, possibly SKI-1. In addition, biochemical and FACS analysis demonstrated that the type-I membrane-bound ACE2 is shed into the medium by a convertase-activated metalloprotease and that such shedding is blocked by dec-RVKR-CMK.

Currently, five major aims are being pursued: (1) To define the importance and site of cleavage by the basic aa-convertases that generate the ~220 and ~80 kDa Sgp products. (2) To determine what enzymes are responsible for the generation of the C-terminal ~110 kDa Sgp product, the processing of human ACE2, and its shedding. (3) To assess if ACE2 regulates the processing of proSg and/or the intracellular trafficking of Sgp and to identify the minimal sequence in ACE2 implicated in the binding of the segment 318-510 of Sgp, reported to be the Sgp binding site to ACE2. (4) Using recombinant Sgp (aa 318-510) and ACE2, the crystal structure of the complex and of each component individually will be obtained (Dr. Pai). (5) Furin and PC7 inhibitors will be identified in combinatorial libraries provided by the BRI (Dr. Menard).

The expertise in fusion proteins, gained through Dr. Pai's recent work on HIV gp41, and its antibody complexes will be very valuable in designing specific anti-fusion peptides that could be tested in cells expressing the SARS-CoV. Dr. Ménard has clearly shown expertise in high throughput combinatorial library screens and is well suited to carry out the identification of convertase inhibitors, with already promising preliminary data for Furin. Inhibitors of Furin or PC7 could be used in multiple other applications *e.g.*, in other viral infections and in cancer. The recent outbreak of the H5N1-type avian flu in Asia is yet another application the convertase-inhibitors will have. With lead compounds and the crystal structure of the Sgp/ACE2 complex in hand, specific pharmaceutical companies will be approached.

PENCE SARS 6: Identification of Compounds Disrupting the Crucial Protein-Protein Interactions in SARS Infection

Principal Investigator/Team Leader: Dr. Shi-Hsiang Shen, McGill University

In this project, the genes encoding for structural proteins S (spike), E (small envelope), M (membrane), and N (nucleocapsid) as well as for a partial RNA-dependent RNA polymerase (Pol) sequence (620 bp) have been synthesized. Presently these synthetic SARS genes have been made available to SARS researchers within the CSRC. These immuno-responsive structural proteins have been used for the development of a diagnostic kit for SARS patients. To this end, S, E, M and N proteins were cloned and expressed in *E.*

coli. Based on these expressed recombinant proteins, a collaborator, International Newtech Development (IND) Inc. (BC), has developed a SARS diagnostic kit for detection of antibodies against these proteins. This kit is currently in review for approval by the State Food and Drug Administration of China. To identify potential therapeutic compounds inhibiting SARS coronavirus, a mammalian reverse two-hybrid system developed in the laboratory is being employed for protein interactions. Small molecules capable of disrupting the key protein-protein interactions required for replication and infection of SARS virus, such as the interactions of N protein with viral M and with the host cellular protein nucleolin, are potential therapeutics for the treatment of SARS. High throughput screening of therapeutic compounds is being performed using drug-like molecule libraries. In addition, two graduate students recently have implemented the RNA interference (RNAi) approach to identify effective small interference RNA (siRNA) primarily against the Pol gene as potential novel therapeutics.

In collaboration with IND, the expressed recombinant structural proteins (E, M, N, and S) have been in commercialization as part of a diagnostic kit. The lead compounds identified in the two-hybrid screening and the effective siRNA sequences are patentable, and could be licensed by companies, such as IND who expressed its interest for a further investment on any potential SARS therapeutics. The technology of siRNA delivery directly from bacteria to mammalian cells will be licensed and transferred to companies.

PENCE SARS 8: Production of Monoclonal Antibodies to Small SARS Proteins

Principal Investigator/Team Leader: Dr. Rachel Roper, East Carolina University

There are seven predicted SARS proteins in the 5 kb near the right terminus of the SARS virus genome that have little or no homology to known proteins (Marra et al., Science, 2003). The terminal location of these genes in the genome suggests that the proteins they encode may be virulence factors, as the central portion of the SARS genome is conserved with other Coronavirus species. In linear viral genomes, essential replication genes are normally conserved in the central region and virulence factors are located near the termini of the genome (Upton et al., J. Virol, 2003). Three of these SARS ORFs are very small (39-63 amino acids) and some have even been excluded from annotation by sequencing groups and are being disregarded because of their size. However, the fact that viral genomes are usually very compact with little intergenic space, the conservation of these genes in SARS isolates (www.sarsresearch.ca), and the presence of upstream transcriptional regulatory sequences (Marra et al., Science, 2003) support the hypothesis that these ORFs are functional in the virus life cycle. Furthermore, five of these proteins have significant hydrophobic regions that are predicted by at least one bioinformatics prediction program to be transmembrane spanning regions, defining a sequence that determines translocation across the ER membrane to produce either an integral membrane protein or a secreted protein. Both secreted and membrane proteins may be significant virulence factors inhibiting immune responses and causing the high mortality in SARS patients. Bioinformatics analysis suggests that some of these proteins possess motifs, which, if functional, would make excellent drug targets.

The objectives of this project are: 1) make monoclonal antibodies to these proteins of interest, 2) determine whether the proteins are made in virus-infected Vero cells, 3) determine where the proteins are localized (secreted into supernatants, ER/Golgi, virus particle, cytoplasmic membrane), and 4) determine what interactions exist between viral proteins or virus/host protein interactions. This information should lead to a basic understanding of the biology of these proteins and yield hypotheses as to the functions of the proteins in the virus life cycle. Every effort will be made not to duplicate existing antibody projects, and PENCE and SAVI will be contacted regularly to keep apprised of such projects. These monoclonal antibodies will be made available to all researchers.

The interaction pathways of these viral proteins will be identified. Monoclonal antibodies to a specific bait protein will be used to immuno-precipitate interacting complexes of proteins from infected cells. The complexes will then be resolved by SDS-PAGE and the interacting proteins will be identified by mass spectrometry at the University of Victoria/Genome BC Proteomics Facility. By this method, both viral protein interactions and host protein interactions will be identified. This information will allow an understanding of the interaction pathways and suggest functions for these viral proteins.

PENCE SARS 9: The SARS Papain-Like Protease: Characterization and Inhibitor Development

Principal Investigator/Team Leader: Dr. Robert Ménard, Biochemistry Dept, University of Montreal, and Biotechnology Research Institute
Co-investigators:
Dr. Lindsay Eltis, Department of Microbiology and Immunology, University of British Columbia
Dr. Enrico Purisima, Biochemistry Department, McGill University

An in-depth analysis of the SARS coronavirus papain-like protease (SCV PL^{pro}) will be performed, with the specific aim of identifying potent lead compounds as putative inhibitors of the enzyme. Knowledge useful to uncover the molecular basis of PL^{pro} activity and specificity will be generated, therefore contributing to the identification and improvement of mechanisms and compounds to alter or inhibit this proteolytic activity. These experiments will benefit from supportive research activities with the papain group of enzymes performed at the Biotechnology Research Institute (BRI). This project will provide numerous opportunities to train and expose postdoctoral fellows and students to multidisciplinary research and technology in an area of importance to Canada, and the results of the studies should provide a valuable framework for the development of drugs to target SARS.

The main objectives for the future are to produce and characterize the SCV papain-like protease, and produce the tools and knowledge to develop inhibitors as lead compounds for drug design. Specifically, five aims will be pursued: (1) Production of the SCV papain-like protease; (2) Development of assays; (3) High-throughput screening for lead generation; (4) Strategies for the design of PL^{pro} inhibitors and production of a structural model for SCV PL^{pro}; and (5) Mechanistic studies.

Results of this study, and in particular the inhibitors generated, should provide a valuable framework for the development of drugs to target SARS. The members of this project have experience in the development and protection (patenting) of novel cysteine protease inhibitors. It is worth mentioning also that the Enzymology Group at the BRI has maintained a high-level of interaction (collaborative and contractual agreements) with industry, as part of the mandate of the National Research Council of Canada.

PENCE SARS 10: Large-Scale Production of the Spike Protein of SARS-CoV for Biochemical, Immunological and Structural Studies.

Principal Investigator/Team Leader: Dr. James Rini, University of Toronto
Co-investigator: Dr. Alan Cochrane, Department of Medical Genetics, University of Toronto

The ultimate goal is to structurally and biochemically characterize the SARS S-protein and its interaction with ACE2. Three different soluble fragments of the S-protein have been produced in a mammalian expression system (each of them containing the ACE2 binding region) and the production of ACE2

fragments is underway. X-ray crystallography will be used to determine the structure of the S-protein and its complex with ACE2, an approach aimed at providing a fundamental understanding of the basis for S-protein mediated host cell attachment and viral fusion.

The various S-protein fragments will also be used to profile the antibodies found in the sera of recovered SARS patients (in collaboration with Dr. David Kelvin, Toronto), an important step in the design of a subunit vaccine. Using novel technology, these fragments will be used to generate neutralizing monoclonal antibodies that will be humanized for use as anti-SARS therapeutics (with Dr. John Schrader, UBC).

Through collaboration both the natural (BC genome centre/Nabil Seidah, Montreal) and codon optimized (Dr. David Kelvin, Toronto) cDNAs of the S-protein of SARS-CoV were obtained, as well as cDNAs coding the S-proteins of HCoV-229E and HCoV-OC43 (Dr. Pierre Talbot, Laval). The codon optimized cDNA was used to make 3x-FLAG constructs designed to express fragments 318-510 and 12-672 as well as a novel fragment 318-577 based on a design created in the laboratory. Since the 318-510 fragment is all that is required to bind to ACE2, it will be a very important reagent for structural and biochemical work as well as in the design of therapeutic antibodies and vaccines. Initial attempts to express a soluble fragment of the S-protein from the natural SARS-CoV cDNA and that of HCoV-229E and HCoV-OC43 were based on the entire extramembranous region. The fragments were cloned into the HGH-HIS tag vector incorporating the puromycin/IRES and expression studies are underway. Anticipating the desire to obtain structural information on the S-protein ACE2 interaction, human ACE2 cDNA was obtained from Dr. Josef Penninger (Toronto). Based on the x-ray crystal structure of ACE, two ACE2 fragments, 18-615 and 18-740, have been selected for expression trials. The first fragment corresponds to the globular protease domain common to ACE, while the second corresponds to the entire extramembranous portion, a region that includes the protease domain and the membrane adjacent collectrin-like domain. Both fragments have been cloned into the 3x-FLAG vector for transient expression studies.

APPENDIX 6:

SUMMARY OF THE SARS RESEARCH PERFORMED BY MITACS

Transmission Dynamics and Spatial Spread of Infectious Diseases: Modeling, Prediction and Control

Principal Investigator/Team Leader: Dr. Jianhong Wu, Laboratory for Industrial and Applied Mathematics, Department of Mathematics and Statistics, York University

Co-Investigators:

Dr. Sten Ardal, Central East Health Information Partnership
Dr. Martin Jack Blaser, Department of Microbiology, New York University School of Medicine
Dr. Fred Brauer, Department of Mathematics, University of British Columbia
Dr. Troy Day, Departments of Mathematics & Biology, Queen's University
Dr. Abba Gumel, Institute of Industrial Mathematical Sciences, Department of Mathematics, University of Manitoba
Dr. Zachary Jacobson, Applied Research and Analysis Directorate, Information, Connectivity and Analysis Branch, Health Canada
Dr. Renjun Ma, Department of Mathematics and Statistics, University of New Brunswick
Dr. Neal Madras, Department of Mathematics and Statistics, York University
Dr. Marcia Rioux, School of Health Policy and Management, Director, York Centre for Health Studies
Dr. Shigui Ruan, Department of Mathematics, Dalhousie University
Dr. Beni Sahai, Cadham Provincial Laboratory, Winnipeg
Dr. Vincent Tao, Geospatial Information and Communication Technology (GeoICT) Lab, Department of Earth and Atmospheric Science, York University
Dr. Pauline van den Driessche, Mathematics and Statistics, University of Victoria
Dr. Glenn Webb, Mathematics Department, Vanderbilt University
Dr. James Watmough, Department of Mathematics and Statistics, University of New Brunswick
Dr. Huaiping Zhu, Laboratory for Industrial and Applied Mathematics, Department of Mathematics and Statistics, York University
Dr. Ping Yan, Modelling and Projection Section, Centre for Infectious Disease Prevention and Control, Population and Public Health Branch, Health Canada
Dr. Michael Mackey, Department of Physiology, McGill University and MITACS Biomedical Theme Leader
Dr. Joseph Morley, Department of Physiology and Centre for Nonlinear Dynamics in Physiology and Medicine, McGill University

The long-term goal is to build a national group focused on the mathematical and statistical modeling and analysis of communicable diseases. The team has broad expertise in epidemiology, virology, statistics, public health policy, GIS, mathematics and scientific computation.

The first short-term goal is to synthesize statistical methods and mathematical models for the analysis of SARS transmission dynamics, in order to provide comprehensive qualitative analysis of various aspects in the outbreak and control of SARS. The team will develop models and methods that incorporate the

critical roles of health care workers, transmission heterogeneity, disease age structure, and super-spreading events. The team will use these methods to evaluate the effectiveness and evolutionary effects of the different control measures, to examine the psychological impact on health care workers and their performance. The second short-term goal is to enhance the understanding of West Nile virus transmission dynamics by developing mathematical models that address issues involving spatial heterogeneity and migration patterns, and the impact of climate changes.

An important achievement has been the formation of a MITACS team focusing on modeling and analysis of communicable diseases, with broad knowledge and capability for a truly interdisciplinary research program, and with strong support and participation from Health Canada. Another important contribution was the Health Canada-MITACS-PIMS Meeting on SARS, September 4-6, 2003, at BIRS (Banff, Alberta). The main purpose of this workshop was to bring together international leaders and active researchers working in the areas related to the modeling, simulations and analysis of the transmission dynamics of SARS and other infectious diseases, to further the fruitful interplay among mathematical, statistical, and epidemiological sciences, in order to speed up the process of finding effective tests and prevention and control measures. This meeting was a success, the meeting generated a 5-page summary of research topics for further study. This helps in bringing close collaboration with Health Canada. For example, MITACS was requested and did provide a report and recommendations to Health Canada on various issues: assessment of control measures and data quality, suggestions for future improvement on data collection and analysis, and public health policy.

During the meeting held in 2003, participants felt the need for another workshop to enhance the collaboration and to train the young generation in a interdisciplinary environment, and this led to the special program sponsored by MITACS-MSRI-PIMS (MSRI is a research center on mathematical sciences founded by National Science Foundation of USA) on mathematical modeling of infectious diseases, which consists of a summer school followed by a research workshop.

APPENDIX 7:

RESEARCH PROPOSAL ABSTRACTS OF FUNDED RESEARCH TEAMS: SARS II—PUBLIC HEALTH AND HEALTH CARE SYSTEM PREPAREDNESS AND RESPONSE TO SEVERE ACUTE RESPIRATORY SYNDROME (SARS): EVALUATION AND LESSONS LEARNED

Legal foundations for a national disease control and surveillance agency in Canada

Principal Investigator: Dr. Tim Caulfield, University of Alberta
The recent SARS outbreak has spurred calls for the creation of a national disease surveillance and control agency in Canada. A proposed federal agency of this type would play a key role in responding to infectious disease outbreaks by undertaking surveillance activities and implementing control measures to halt the spread disease. However, the nature and extent of the legal authority of the federal government to establish such a body is a critical question that must be answered. To address this issue, the primary objectives of this research proposal are to: (1) identify and describe the legal foundations necessary to create a national disease surveillance and control body in Canada; and (2) analyse legal issues that may define the mandate and constrain the power of such a body. The first part of this research will identify federal powers in relation to public health and the second part will focus on the legal authority of a federal agency to conduct surveillance and impose control measures such as quarantine orders and mandatory screening. This research will be informed by the recent Canadian experience with SARS and will result in a comprehensive legal analysis that will assist legislators, policy-makers and public health officials make decisions about how to prepare at a national level for the next infectious disease outbreak.

The effect of the Ontario SARS outbreak on population mortality

Principal Investigator: Dr. Stephen Hwang, St. Michael's Hospital (Toronto)
During the recent SARS outbreak in Ontario, the need for extraordinary infection control measures resulted in a period of extremely restricted access to hospital-based health care for the residents of Toronto. It is not known if this limited access to health care resulted in higher death rates in Toronto, completely distinct from deaths that were directly due to SARS. This study will use information from death certificates and the census to determine if death rates due to causes other than SARS went up or down during the SARS outbreak. This question is important, because the closure of hospitals may again be necessary in the event of future infectious disease outbreaks. Public health officials need to understand if these closures cause "collateral damage" to people's health, and if so, develop plans to reduce these unintended adverse consequences.

Optimizing clinical and public health management of influenza-like-illnesses of undetermined etiology in a world changed by SARS

Principal Investigator: Dr. Kamran Khan, St. Michael's Hospital (Toronto)
SARS is a newly identified infectious disease which rapidly disseminated around the globe with devastating health and economic consequences. In June 2003, the World Health Organization declared that SARS had been contained worldwide, but many fear that it might reemerge in future flu seasons. This scenario is particularly worrisome since many of the symptoms of SARS overlap with those of

influenza and other common flu-like illnesses. Given that the diagnosis of SARS is established upon a combination of symptoms, epidemiological links to other SARS cases, and lab tests, healthcare providers would be forced to rely upon the latter two factors to make their diagnosis during flu season. Unfortunately, an outbreak of SARS during flu season could quickly overwhelm healthcare resources and seriously delay public health efforts to establish critical epidemiologic links to other SARS cases. The current lack of a widely available, rapid, and highly sensitive test for SARS compounds this diagnostic problem. This study will involve the development of mathematical models or simulations that will identify the most efficient and cost-effective methods of controlling a future outbreak of SARS, with emphasis on doing so in the setting of peak flu season. The study will evaluate numerous containment strategies from the most high tech to the most basic, so that effective strategies could be employed even if healthcare resources are stretched to their limits. The results of this study will be extremely useful to front line healthcare providers evaluating patients with flu-like illnesses. Defining the most efficient means to contain an outbreak of SARS today will ensure that should SARS return in the future, a well defined roadmap exists to facilitate a uniform and effective response by the healthcare profession.

Psychological and occupational impact of the SARS outbreak on healthcare workers

Principal Investigator: Dr. Robert Maunder, Mount Sinai Hospital
The outbreak of SARS in Toronto and the surrounding regions, beginning in February 2003 was an extraordinary event in the life of the city and, especially its hospitals. This study assesses the psychological impact of the SARS outbreak on professionals working in hospitals. In particular we will determine the how common it is for professional hospital workers to be suffering from psychological symptoms such as depression, anxiety and sleep disturbance 6 to 18 months after the outbreak. We will also study other possible effects of SARS exposure such as job burnout and professionals choosing to reduce their hours or to change their jobs. We have already completed an initial survey of some of these outcomes in about 1,600 healthcare workers at 3 hospitals. We propose to study the effects of SARS more systematically in this study. Based on the results of the completed survey we plan to measure psychological outcomes in inpatient nurses, emergency department workers, intensive care unit workers and hospital administrators. Professionals in these roles in Toronto during the SARS outbreak will be compared to similar workers in Hamilton, which was not directly affected by SARS.

Economic evaluation of direct medical and non-medical costs associated with the SARS outbreak

Principal Investigator: Dr. Nicole Mittman, Sunnybrook & Women's College Health Sciences Centre
This study will investigate the incremental direct costs associated with the management of Severe Acute Respiratory Syndrome (SARS) from the hospital perspective. Direct costs will be divided into MEDICAL and NON-MEDICAL costs. Direct medical costs will be calculated by comparing the costs associated with the management of SARS patients admitted to Sunnybrook and Women's College Sciences Centre (SWCHSC) during the SARS outbreak period (March 13 to August 13, 2003) and a comparator group of community acquired pneumonia (CAP) patients admitted one year prior to the SARS outbreak. Resource utilization variables (hospitalization, personnel, treatment, procedures, diagnostics/laboratory, supplies and infection control directives) will be collected via chart extraction of inpatient and outpatient medical records. Unit costs for the resources will be determined by examining SWCHSC financial records, human resources and hospital drug formulary and calculated in 2003 CAN$. An incremental direct medical cost will be calculated [Total direct MEDICAL costs for SARS (N=75) minus Total direct MEDICAL costs for CAP (N=75)]. Direct NON-MEDICAL costs (screening, precautions, human resources) were determined

by comparing the infectious control measures instituted at SWCHSC during the outbreak period in 2003 to NON-MEDICAL costs in a 2002 pre-SARS period. Resource and costing data will be obtained from financial records, human resources, manufacturing and public affairs. An incremental direct non-medical costs will be calculated [Total direct NON-MEDICAL costs of SARS minus Total direct NON-MEDICAL costs of pre-SARS].

Exploring the psychosocial and health service consequences of SARS on children and their families: lessons learned for pediatric health care practice and policy

Principal Investigator: Dr. David Nicholas, Hospital for Sick Children
Severe Acute Respiratory Syndrome (SARS) was an unprecedented public health crisis, affecting particularly Canadians living in Toronto. Whereas SARS more directly affected adults and health care professionals who work in adult hospitals, little is known about the human impact of SARS and SARS-related infection control measures on children with chronic health conditions and their families. SARS-related infection control measures such as isolation, restricted family visitation policies, masks and gowns, and reduced access to services, for example, significantly changed a family-centred approach to care in children's hospitals and children's community health care. Our clinical experience suggests that children and families experienced: isolation, loneliness, anxiety, financial stress, and reduction in services. This study will be the first to explore the psychosocial and the service delivery consequences of SARS on Canadian children with illnesses such as asthma, cardiac disease, cystic fibrosis and other complex and potentially life threatening conditions. This knowledge along with a consensus building process with Canadian and international experts will lead to recommendations for best practices for caring for chronically ill children during times of public health crisis.

The spread and evolution of SARS coronaviruses through contact networks: prediction, recognition and control

Principal Investigator: Dr. Babak Pourbohloul, University of British Columbia
More than eighteen months since the first case of severe acute respiratory syndrome (SARS) occurred in Guangdong province of China its pattern of spread remains enigmatic and appropriate control measures for future outbreaks are not yet established. Although SARS cases occurred in several hospitals and cities worldwide, only a handful progressed into sizable outbreaks. We propose to use mathematical modeling and bioinformatics to address questions about the heterogeneous spectrum of SARS illnesses; to predict the future course of SARS for the most probable scenarios; and to quantitatively assess the impact of various control measures for each scenario. In particular we seek to answer four questions: Will SARS return? If so, how will it return? How can we best recognize it should it return? And, how can we best control its spread should it return? To answer these questions, we will build the mathematical methods and develop a novel transmission signature methodology, a companion to molecular fingerprinting that identifies infectious pathogens based on the observed patterns of transmission and clustering. We have assembled a national team to advance the development of these predictive tools in order to answer challenging questions regarding the possibility of reemergence of SARS. As a multidisciplinary team, we will design and build several template models for predicting of SARS transmission in "realistic" settings, which will enable us to make specific recommendations for future introductions of SARS in these settings, extract general SARS intervention guidelines that apply across diverse settings, and establish a versatile infrastructure that can be readily adapted to address the spread and control of other respiratory-borne pathogens.

Determining the population health impact of the healthcare system response to SARS outbreak

Principal Investigator: Dr. Michael Schull, Sunnybrook & Women's College Health Sciences Centre
The outbreak of Severe Acute Respiratory Syndrome (SARS) in Toronto is an event that is unprecedented since the introduction of Medicare in Canada. In addition to causing critical illness and death, efforts to control the spread of SARS resulted in significant and widespread restrictions on access to the healthcare system. While these measures appear to have been effective in controlling the spread of the outbreak into the community, these efforts may also have resulted in unintended health consequences in the non-SARS population. The goal of this study is to determine the population health impact of the health care system restrictions imposed to control the SARS outbreak. We will describe the utilization of healthcare services (*e.g.* physician visits, hospital admissions, ambulance transfers, medication prescriptions) before, during and after the SARS outbreak; identify whether specific patient groups suffered due to reduced access to hospital or ambulatory medical care; identify other patient groups that may have been unaffected by the SARS-imposed healthcare restrictions; and develop specific, clear and simple policy recommendations applicable to general healthcare settings which may help reduce any negative impact of widespread health care system restrictions in the future. Our results and recommendations should be applicable to other healthcare settings, inside and outside Canada, experiencing similar restrictions on health care services, whether these are imposed due to an infectious disease outbreak, a bioterrorism attack or other major disruption to the health system infrastructure.

Ethical challenges in the preparedness and response for SARS

Principal Investigator: Dr. Ross Upshur, Sunnybrook & Women's College Health Sciences Centre
In March and April of 2003, the outbreak of Severe Acute Respiratory Syndrome (SARS) put enormous pressures upon public health institutions, governments and ordinary citizens. There are many ethical issues raised by the SARS epidemic including 1) the ethics of quarantine and the use of restrictive measures upon health care workers and patients 2) the collateral damage of SARS, the lack of access for non-SARS infected patients to basic medical care and the resources allocated to combat the epidemic 3) the 'duty to care' for SARS infected patients by the health care community 4) SARS and Globalization, the context of infectious disease within our new global framework. On the basis of these four primary themes, this research proposal will examine each principle with mixed method approaches in order to understand ethical implications of SARS and to shed new light onto the area of emerging infectious diseases. The results of this research study will act as a guide for health care professionals, policy makers and academic institutions. It will also serve as a blueprint to foster further discussion into the management of disease control and put the global health care community into a unifying context.

Barriers and facilitators to implementing protective measures against SARS for healthcare workers: a collaborative interdisciplinary study

Principal Investigator: Dr. Annalee Yassi, University of British Columbia
The global outbreak of Severe Acute Respiratory Syndrome (SARS) strained health care resources in Ontario, British Columbia (BC) and elsewhere, and it appeared that basic workers infection control and occupational health principles were not clearly understood or consistently applied across healthcare systems. Our interdisciplinary team will generate important new knowledge to protect healthcare workers (HCWs) from SARS and other pathogens. In this 4-phased cross-sectional study we will characterize SARS-related behavioural intentions of HCWs regarding compliance with protective measures, and ability

and willingness to treat SARS patients and to accept quarantine. We will explore environmental, organizational and individual determinants of HCW intentions by conducting focus groups of front-line HCWs, and of individuals responsible for implementing control measures. We will then survey over 1800 HCWs in BC and 750 Ontario nurses, and we will conduct workplace audits in the 2 BC health authorities most affected by the outbreaks to assess their organizational and environmental ability to prevent future outbreaks. Strong ties exist to disseminate the findings to those who would benefit in BC, Ontario and beyond.

APPENDIX 8:

PUBLICATIONS AND MANUSCRIPTS IN PRESS, SUBMITTED OR IN PREPARATION

CIHR Institute of Infection and Immunity

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SARS I

Loeb Research Team

Diagnostic

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Skowronski Research Team

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Dennis Research Team

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Bergeron Research Team

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PENCE SARS 2

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APPENDIX 9:

PATENTS ISSUED

Dennis Research Team

Ashkenas et al. Novel uses of restriction enzymes to neutralize DNA contamination in PCR and RT-PCR. (patent application)

PENCE SARS 2

Brown, E., Eltis, L.D., Cechetto, J., Blanchard, J., Elowe, N., Fortin, P.D. and Huitema, C. Inhibitors of the Severe Acute Respiratory Syndrome coronavirus main proteinase. Provisional patent filed March, 2004 in Canada. (UBC file no: 04-008)

PENCE SARS 3

Rapid and general profiling of viral protease specificity using microarrays of fluorogenic peptidyl substrates and libraries of internally quenched fluorogenic substrates. Inventors: François Jean. UBC invention disclosure #04-044, filed August 18, 2003.

APPENDIX 10:

PRESENTATIONS

CIHR Institute of Infection and Immunity

Singh, B. SARS conference, Toronto, April 30-May 1, 2003.

Singh, B. Canada/China/Hong-Kong Collaborations in SARS Research Teleconference, May 15, 2003.

Singh, B. SARS: Developing a research response. Bethesda, MD, May 30, 2003.

Singh, B. SARS Telethon, Toronto, June 5-6, 2003.

Singh, B. Canadian SARS Research Consortium Meeting, Toronto, July 25, 2003.

Singh, B. Regulatory Issues Associated with the Development and Licensing of SARS Vaccines and Immmunotherapy Products Workshop, Ottawa, August 18-19, 2003.

Singh, B. Healthcare Emergency Preparedness Summit, Toronto, November 24-25, 2003.

Singh, B. Current Science of SARS Symposium, Winnipeg, December 1-2, 2003.

Singh, B. CSRC patient sample meeting, Toronto, December 8, 2003.

Singh, B. International Conference on SARS- one year after the outbreak, Lubeck, Germany, May 8-11, 2004.

Loeb Research Team

Diagnostic

Tang, P., Louie, M., Richardson, S., et al. Laboratory diagnosis of severe acute respiratory syndrome (SARS) in Canada. Abstract V-485a. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 14-17, 2003.

Mahony, J., Petrich, A., Louie, L., et al. Comparison of the cost and performance of seven RT-PCR assays for detection SARS coronavirus RNA. Abstract V-796d. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 14-17, 2003.

Smieja, M., McNally, C., Loeb, M., Fearon, M., Burton, L., Haley, A., Suggett, B., Taha, M. Richardson S. for the Ontario Laboratory Working Group for the Rapid Diagnosis of Emerging Infections. Individual and cluster sensitivity of respiratory virus testing in institutional outbreaks. ICAAC, Washington, DC, Oct. 30-Nov. 2, 2004.

Fuller, J., Tang, P., Skrastins, R., et al. A Community cluster of severe acute respiratory syndrome (SARS). Abstract SP1, p. 80. 2003 Conjoint Meeting of CACMID & AMQ, Canadian Association for Clinical Microbiology and Infectious Diseases, Montreal, November 2-5, 2003.

Mahony, J., Petrich, A., Louie, L., et al. Comparison of performance and cost of seven PCR assays for the detection of SARS coronavirus RNA in clinical specimens. Abstract A5, p. 27. 2003 Conjoint Meeting of CACMID & AMQ, Canadian Association for Clinical Microbiology and Infectious Diseases, Montreal, November 2-5, 2003.

Petrich, A.K., Mahony J., Chong S., et al. Multicentre evaluation of seven SARS coronavirus RT-PCR assays. Abstract A4, p. 26. 2003 Conjoint Meeting of CACMID & AMQ, Canadian Association for Clinical Microbiology and Infectious Diseases, Montreal, November 2-5, 2003.

Mahony, J.B., Petric, M., Hall, A., et al. Rapid detection of SARS-CoV IgG and IgM antibody in human and animal sera by a Novel Immunodot Assay. Abstract 01798. 11th International Congress of Infectious Diseases, Cancun, Mexico, 2004.

Mahony, J.B., Petrich, A., Chong, S., et al. Evaluation of three commercial nucleic acid amplification tests (NAAT) for detection of SARS-CoV RNA. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, October 30-November 2, 2004.

Mahony, J., DeKoning, L., Spafford, R., Petric, A., Smieja, M., Chernesky, M., Petric, M. and Richardson, S. Ontario Laboratory Working Group for the Rapid Diagnosis of Emerging Infections. Development of a novel amplified ELISA for the detection of SARS coronavirus IgM, IgG and IgA antibody. Pan American Society for Clinical Virology, Clearwater, FL, April 23-24, 2004.

Johnson, G., Gharabaghi, F., Adachi, D., Draker, R., Ayers, M., Talbot, P.J., Richardson, S. and Tellier, R. Ontario Laboratory Working Group for the Rapid Diagnosis of Emrerging Infections. Detection by RT-PCR of coronaviruses, including SARS, and optimization of RNA recovery from clinical samples. Pan American Society for Clinical Virology, Clearwater, FL, April 23-24, 2004.

Petrich, A., Mahony, J., Chong, S., Broukhanski, G., Gharabaghi, F., Johnson, G., Louie, L., Luinstra, K., Willey, B., Louie, M., Jamieson, F., Mazzulli, T., Tellier, R., Smieja, M. and Richardson, S. Ontario Laboratory Working Group for the Rapid Diagnosis of Emerging Infections. Comparison of nucleic acid extraction methods for detection of SARS RNA in stool samples. Pan American Society for Clinical Virology, Clearwater, FL, April 23-24, 2004.

Petrich, A., Mahony, J., Chong, S., Broukhanski, G., Gharabaghi, F., Johnson, G., Louie, L., Luinstra K., Willey, B.M., Chui, L., Jamieson, F., Karnauchow, T., Louie, M., Mazzulli, T., Petric, M., Tellier, R., Smieja, M. and Richardson, S. Ontario Laboratory Working Group for the Rapid Diagnosis of Emerging Infections. Multicentre evaluation for detection of SARS coronavirus nucleic acid in stool samples. Pan American Society for Clinical Virology, Clearwater, FL, April 23-24, 2004.

Smieja, M., Mahony, J., Petric, M., Mazzulli, T., Fearon, M., Hawes, G., Dick, D., Booth, T., deKoning, L., Spafford, R., Haynes, L. and Richardson, S. Ontario Laboratory Working Group for the Rapid Diagnosis of Emerging Infections. Inter-laboratory comparison of SARS serologic testing. Pan American Society for Clinical Virology, Clearwater, FL, April 23-24, 2004.

Tansey, C.M., Gold, W.L., Louie, M., Loeb, M., Muller, M.P., deJager, J., Brunton, J., Mazzulli, T., Walmsley, S., Rachlis, A., Mederski, B.D., Silverman, M., Levinsky, R., Shainhouse, Z., Downey, T., Styra, R., Webster, P., Zamel, N., Richardson, S., Slutsky, A., Herridge, M.S. Canadian SARS Research Network. Three-month pulmonary, functional and quality of life outcomes in survivors of the severe acute respiratory distress syndrome (SARS). 100th International Conference of the American Thoracic Society Meeting, Orlando, FL, May 21-26, 2004.

Mahony, J., Petrich, A., Chong, S., Smieja, M., Chernesky, M. and Richardson, S. The Ontario Laboratory Working Group for the Rapid Diagnosis of Emerging Infections. Evaluation of three commercial nucleic acid amplification tests (NAAT) for detection of SARS-CoV RNA. 104th General Meeting of the American Society for Microbiology, New Orleans, LA, May 23-27, 2004.

Richardson, S. Severe Acute Respiratory Syndrome. Bontario Conference 2003, LA, November 13, 2003

Richardson, S. Laboratory issues and infection control. Infection Control Precautions for Respiratory Infections, Health Canada Meeting, November 24, 2003.

Richardson, S. Laboratory diagnostics of SARS – research issues. Current Science of SARS Symposium, Health Canada and CIHR, December 1, 2003.

Richardson, S. Diagnostic Testing for SARS – CoV: An Update. The Society for Healthcare Epidemiology of America's (SHEA) 14th Annual Scientific Meeting, April 17, 2004.

Richardson, S. Rapid Diagnostic Testing for Emerging Pathogens. CIDS/CAMM/CHICA Conference, April 29, 2004.

Richardson, S. SARS in Toronto: Advances in laboratory diagnostics. DPLM Research Day, The Hospital for Sick Children, June 10, 2004.

Clinical

Louie M., Herridge M., Tansey C., Loeb M., Styra R., Gold W. and deJager J. Long Term Outcomes of SARS. Health Canada SARS Symposium, Winnipeg, December 2003.

Tansey, C.M., Gold, W.L., deJager, J., Muller, M., Rachlis, A., Mederski, B.D., Mazzulli, T., Stainhouse, Z., Styra, R., Webster, P., Zamel, N., Loeb, M., Richardson, S., Louie, M., Slutsky, A., Herridge, M.S. Canadian SARS Research Network Three Month Pulmonary, Functional and Quality of Life Outcomes in Survivors of the Severe Acute Respiratory Distress Syndrome (SARS). Annual American Thoracic Society Meeting, May 2004

Styra, R., Gold, W., Robinson, S., Hawryluck, L., Simor, A., Rachlis, A., Phillips, J., Offner, M., Green, K. and Low D. Post-traumatic Stress Disorder and Quality of Life in Patients Diagnosed with SARS. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, September 14-17, 2003

Pathology

Mazzulli, T., Farcas, G., Willey, B., Low, D.E., Kain, K., Tellier, R., Johnson, G., Richardson, S., Gold, W. and Poutanen, S.M. Detection of Severe Acute Respiratory Syndrome-Associated Coronavirus in Lung Tissue By Reverse-Transcription PCR. Abstract V-484. 43rd ICAAC, Chicago, Illinois, 2003.

Farcas, G.A., Mazzulli, T., Willey, B.M., Poutanen, S.M., Butany, J., Low, D.E., Asa, S.L, Faure, P., Akvavan, P., Moussa G. and Kain K. C. Fatal Severe Acute Respiratory Syndrome is Associated with Multi-organ Involvement by Coronavirus (SARS-CoV). Abstract K-1315b. 43rd ICAAC, Chicago, Illinois, 2003.

Butany, J., Poutanen, S., Low, D., Ghazarian, D. and Asa S. Pathologic Findings in Human Tissues from Cases of Severe Acute Respiratory Syndrome in Toronto. United States and Canadian Academy of Pathology 93rd Annual Meeting, Vancouver, British Columbia, 2004.

Hwang, D.M., Chamberlain, D.W., Poutanen, S.M., Asa, S.L. and Butany J.W. A Detailed Analysis of Pulmonary Pathology in the Severe Acute Respiratory Syndrome in Toronto. United States and Canadian Academy of Pathology 93rd Annual Meeting, Vancouver, British Columbia, 2004.

Epidemiology

Loeb, M., Henry, B., Ofner, M., Rose, D., Hwlyka, T., Levie, J., McDonald, J., Smith, S., Moss, L., Smith, A., Green, K. and Walter, S. Risk factors for severe respiratory syndrome among critical care nurses. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, September 14-17, 2003.

Scales, D.C., Green, K., Chan, A.K., Poutanen, S.H., Nowak, K., Foster, D., Raboud, J., Saskin, R., Heselgrave, R., McGeer, A.J. and Stewart, T.E. SARS exposure in an Intensive Care Unit: Level of Exposure and Syndrome Development in Health Care Workers. 43rd ICAAC, Chicago, Illinois, September 14-17, 2003.

Gold, W., et al. Seroprevalence of antibiotics to SARS CoV in exposed health care workers in Toronto. 43rd ICAAC, Chicago, Illinois, September 2003.

Host Immune Response

Cameron, M.J., Gold, W., Dresser, L., Ran, L., Poutanen, S., Louie, M., Phillips, E., Mederski, B., Loufty, M., Mazzulli, T., Willey, B., Muller, M., Persad, D., Xu, L., Brunton, J., Low, D., McGeer, A. and Kelvin D.J. The Canadian SARS Research Network. Identification of Gene Expression Profiles in Patients with Severe Acute Respiratory Syndrome (SARS) that may be Predictive of Diagnosis, Severity and Clinical Outcome of the Illness. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, September 14-17, 2003.

Cameron, M.J., Dresser, L., Poutanen, S., Willey, B., Womsley, S., Persad, D., Gold, W., Phillips, E., Louie, M., Rachlis, A., Brunton, J., Kashavjee, S., Low, D. and Kelvin, D.J. The Canadian SARS Research Network. Bi-Phasic Cytokine Profiles During the Course of Severe Acute Respiratory Syndrome (SARS). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Chicago, IL, September 14-17, 2003.

Cameron, M.J., Danesh, A., Persad, D., Ran, L., Xu, L., Gold, W., Dresser, L., Poutanen, S., Louie, M., Phillips, E., Mederski, B., Loufty, M., Mazzulli, T., Willey, B., Muller, M., Brunton, J., McRitchie, D., McGeer, A., Loeb, M. and Kelvin, D.J. Immune Responses in Patients with Severe Acute Respiratory Syndrome (SARS): Lessons from Cytokine and Gene Expression Profiling, FACS Analysis, and Epitope Mapping. Keystone Symposia on Bioterrorism and Infectious Disease, Keystone, CO, January 6-11, 2004.

Persad, D., Cameron, M.J., Danesh, A., Kelvin, A., Gold, W., Dresser, L., Poutanen, S., Louie, M., Keshavjee, S., Phillips, E., Mederski, B., Loufty, M., Mazzulli, T., Willey, B., Muller, M., Brunton, J., McRitchie, D., McGeer, A., Loeb, M. and Kelvin, D.J. The CXCL10-CXCR3 loop is deregulated in SARS infected individuals. Keystone Symposia on Bioterrorism and Infectious Disease, Keystone, CO, January 6-11, 2004.

Humar, A. SARS and West Nile Virus in Transplant. State of the Art Lecture. ATC Meeting, Boston, MA., May 2004.

Kumar, D., Farcas, G., Uy, K., Levy, G., Kain, K. and Humar A. SARS in Transplantation: Clinical and virologic findings. ATC Meeting, Boston, MA, May 2004.

Dennis Research Team

Dennis, J., Fish, E., Siminivitch, K. and Ho, C.-Y. CSRC SARS Research meeting Toronto, July 25, 2003.

Fish, E. Therapeutic potential of interferon alfacon1 plus corticosteroids in SARS. Cytokines, Signaling and Diseases. ISICR Annual meeting. Cairns, Australia, Oct. 2003

Fish, E. Type 1 interferons: more than just antivirals. La Jolla Institiute for Allergy and Inflammation, San Diego, December 12, 2003.

Fish, E. Therapeutic potential of interferon alfacon-1 in SARS. WHO Conference, Geneva, October 23, 2003.

Fish, E. Towards understanding the complexity of interferons as therapeutics. Intermune, Brisbane California, March 23, 2004.

Skowronski Research Team

Babiuk, L. Efficacy of SARS vaccines in Animal Models for SARS. American Society for Virology Meeting, Montreal, July 14, 2004.

Brunham, R.C. SAVIs response to SARS: can we rapidly make a human vaccine? Department of Molecular Biology and Biochemistry, Simon Fraser University, March 2004.

Brunham, R.C. SAVIs response to SARS: can we rapidly make a human vaccine? Canadian Institute for Academic Medicine, Halifax, N.S., April 2004

Gold, W.L., Mederski, B., Rose, D., Simor, A., Minemma, B., Mahoney, J., Petric, M., MacArthur, M., Willey, B.M., Chua, R., Pong-Porter, S., Rzayev Y., Tamlin, P., Henry, B., Green, K., Low, D.E., Mazzulli, T. Prevalence of Asymptomatic (AS) Infection by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in Exposed Healthcare Workers (HCW). ICAAC, Chicago, 2003.

Johnson, G., Adachi, D., Draker, R., Ayers, M., Talbot, P.J. and Tellier R. Detection by RT-PCR of the SARS Coronavirus and of Other Human Coronaviruses. 71st Conjoint Meeting on Infectious Diseases (CACMID), Montréal, November 2003.

Johnson, G., Gharabaghi, F., Adachi, D., Draker, R., Ayers, M., Talbot, P.J., Richardson, S., Tellier, R., and the Ontario Laboratory Working Group for the Rapid Diagnosis of Emerging Infections. Detection by RT-PCR of coronaviruses including SARS, and optimization of RNA recovery from clinical samples. 20th Annual Clinical Virology Symposium, Clearwater, Florida, 2004.

Mazzulli, T., Chua, R., Kreiswirth, N., Pong-Porter, S., Rzayev, Y., Ahkaven, P., McGeer, A., Petric, M., Mahony, J. and Willey, B.M. Comparison of Euroimmune IFA and ELISA assays for the detection of IgG antibodies against SARS-CoV in serum. 20th Annual Clinical Virology Symposium, Clearwater, Florida, 2004.

Meyers, L.A. Texas Department of Health. October 2003.

Meyers, L.A. University of Texas Dean's Scholars Seminar. November 2003.

Meyers, L.A. Santa Fe Institute, Business Network and Board of Trustees Annual Meeting. November 2003.

Petric, M., Mak, A., Goh, S.H., Karunakaran, K., Chow, R., Lawrence, D., Shivji, R., McNabb, G., Skowronski, D., Krajden, M., Brunham, R. Diagnostic Tests for SARS-Cornavirus. CACMID, Montreal, 2003.

Petrich, A., Mahony, J., Chong, S., Broukhanski, G., Gharabaghi, F., Johnson, G., Louie, L. Luinstra, K., Kreisworth, N., Willey, B.M., Chui, L., Jamieson, F., Karnauchow, T., Louie, M., Mazzulli, T., Petric, M., Tellier, R., Smieja, M., Chernesky, M., Poutanen, S. and Richardson, S. Multicentre evaluation for detection of SARS coronavirus nucleic acid in stool specimens. 20th Annual Clinical Virology Symposium, Clearwater, Florida, 2004.

Pourbohloul, B. Infectious Disease Grand Rounds, University of British Columbia, March 2004.

Skowronski, D.M. SAVI: The SARS Accelerated Vaccine Initiative. WHO Conference on SARS Research, Singapore, June 19, 2003.

Skowronski, D.M. SIVI and SAVI: the Yin and Yang of emergency vaccine development. International Science Symposium on SARS. Beijing, China, July 10-11, 2003

Skowronski, D.M. SAVI: SARS Accelerated Vaccine Initiative. Quebec SARS Scientific Committee, Montreal, September 2003.

Skowronski, D.M. Anxious foresight: how BC contained SARS. BC Pharmacy Association, Penticton, BC, October 2003.

Skowronski, D.M. Anxious foresight: how BC contained SARS. Ontario Hospital Association, Toronto, Ontario, October 2003.

Skowronski, D.M. Anxious foresight: how BC contained SARS. Quebec Ministry of Health, Montreal, November 2003.

Skowronski, D.M. and the SAVI Consortium. The SARS Accelerated Vaccine Initiative (SAVI): A framework for emergency vaccine discovery. Seventh Annual Conference on Vaccine Research. National Foundation for Infectious Diseases, Arlington, VA, May 2004.

Skowronski, D.M. Emerging pathogens. Think Again, 2004 – Millennium Excellence Award Program. Ottawa, Ontario, September 2004.

Skowronski, D.M. Failed outbreak and successful containment of SARS in BC, Canada. CACMID, Regina, November 2004.

Skowronski, D.M. How BC responds to emerging respiratory-borne pathogens. Quebec Annual Public Health Days. Montreal, December 2004.

Smieja, M., Mahony, J., Petric, M., Mazzulli, T., Fearon, M., Hawes, G., Dick, D., Booth, T., DeKoning, L., Spafford, R., Hayes, L. and Richardson, S. Inter-laboratory comparison of SARS serologic testing. 20th Annual Clinical Virology Symposium, Clearwater, Florida, 2004.

Tipples, G.A., Drebot, M.A., Bastien, N., Li, Y., Jones, S., Feldman, H., Kabani, A., Booth, T., Andonov, A., Fearon, M., Jamieson, F., Isaac-Renton, J., Krajden, M., McNabb, A., Petric, M. and Plummer, F. Analysis of SARS-associated coronavirus laboratory testing at the National Microbiology Laboratory. CACMID, Montreal, 2003.

SAVI

Skowronski, D.M. and the SAVI Consortium. The SARS Accelerated Vaccine Initiative (SAVI): A framework for emergency vaccine discovery. Seventh Annual Conference on Vaccine Research. National Foundation for Infectious Diseases. Arlington, Vermont, May 2004.

Shaw, L.D, Ramotar, K., Petric, M. and Karnauckow, T.M. Evaluation of the Realart HPA coronavirus LC RT-PCR (Artus) and the Light Diagnostics SARS Oligodetect (Chemicon) assays for the detection of SARS coronavirus RNA. 20th Annual Clinical Virology Symposium, Clearwater, Florida, 2004.

Mahony, J., DeKoning, L., Spafford, R., Petrich, A., Smieja, M., Chernesky, M., Petric, M. and Richardson S. Development of a novel amplified ELISA for the detection of SARS coronavirus IgM, IgG and IgA antibody. 20th Annual Clinical Virology Symposium, Clearwater, Florida, 2004.

Smieja, M., Mahony, J., Petric, M., Mazzulli, T., Fearon, M., Hawes, G., Dick, D., Booth, T., DeKoning, L., Spafford, R., Hayes, L. and Richardson, S. Inter-laboratory comparison of SARS serologic testing. 20th Annual Clinical Virology Symposium, Clearwater, Florida, 2004.

Mazzulli, T., Chua, R., Kreiswirth, N., Pong-Porter, S., Rzayev, Y., Ahkaven, P., McGeer, A., Petric, M., Mahony, J. and Willey, B.M. Comparison of Euroimmune IFA and ELISA assays for the detection of IgG antibodies against SARS-CoV in serum. 20th Annual Clinical Virology Symposium, Clearwater, Florida, 2004.

Meyers, L.A. Brown University, February 2004.

Meyers, L.A. University of Texas, LAMP. February 2004.

Meyers, L.A. Mathematical Sciences Research Institutes (MSRI), Annual Meeting of Academic Sponsors. March 2004.

Meyers, L.A. Los Alamos National Laboratories. May 2004.

Meyers, L.A. Sandia National Laboratories. May 2004.

Pourbohloul, B. Infectious Disease Grand Rounds, University of British Columbia. March 2004.

Babiuk, L. American Society for Virology Meeting, Montreal, July 14, 2004. Efficacy of SARS vaccines in Animal Models for SARS.

Finlay, B. WHO meeting on SARS, Geneva, October 2003.

Gauldie, J. World Vaccine Congress Meeting, Montreal, April 2004.

CANVAC

Kelvin, D. Case study on reverse vaccinology-how genomics affects vaccine development: World Vaccine Congress 2003, Montreal, April 7-9, 2003

Kelvin, D. Immune Modeling of Infectious Diseases, 2nd Annual Conference of Genomics Researchers, Montreal, April 30, 2003.

Kelvin, D. Cytokine and Gene Expression Profiling in SARS Patients: Modeling of Immune Responses, Canvac annual meeting, June 4, 2003.

Kelvin, D. Immunological Aspects of SARS: Health Canada- SARS Technical Workshop, Ottawa, August 17, 2003.

Kelvin, D. Funtional Genomics Pharmacogenomics and Proteomics of the Immune System, the SARS experience. Genome Canada's National Genomics and Proteomics Symposium, Toronto, Sept. 25, 2003.

Kelvin, D. Immunological Responses in SARS Patients: Cytokine and Gene Expresion. International workshop of Emerging Infectious Diseases, Hangzhou, China, Oct. 25, 2003.

Kelvin, D. Immunological Aspects of SARS: Cytokine and Gene expression profiles define onset and course of illness. International Conference on SARS and Flu, Taipei, Taiwan, Oct. 28, 2003.

Kelvin, D. Immunological Aspects of SARS: Cytokine and Gene Expression Profiles Define Onset and Course of Illness. WHO Consultation on Needs and Opportunities for SARS Vaccine Research and Development, Geneva, Oct. 31, 2003.

Kelvin, D. Cytokine and Gene Expression Profiling in SARS Patients: Modeling of Immune Responses and Vaccine Generation. Infectious Diseases Rounds – University Health Network, Toronto, Nov. 4, 2003.

Kelvin, D. Cytokine and Gene Expression Profiling in SARS Patients: Modeling of Immune Responses and Vaccine Generation. BioNorth 2003 International Conference & Exhibition, Ottawa, Nov. 18, 2003.

Kelvin, D. Cytokine and Gene Expression Profiling in SARS Patients: Modeling of Immune Responses and Vaccine Generation. Crucell-Leiden, Amsterdam, Nov. 20, 2003.

Kelvin, D. Immune responses in patients with Severe Acute Respiratory Syndrome (SARS): Lessons from Cytokine & Gene Expression Profiling, FACs Analysis and Epitope Mapping. Genome 2003 Symposium, Taipei, Taiwan, Dec. 8, 2003.

Kelvin, D. Gene and Cytokine Profiling: National Microbiological Laboratories. Winnipeg, Jan. 6, 2004.

Kelvin, D. Immune Responses in Patients with SARS: Lessons from Cytokine and Gene Expression Profiling, FACS Analysis and Epitope Mapping, Keystone Symposium, Colorado, Jan. 9, 2004.

Kelvin, D. WHO- Technical Meeting on SARS Animal Models in collaboration with Professor Albert Osterhaus- Erasmus University. Rotterdam, The Netherlands, Feb 5, 2004.

Kelvin, D. Genomics and proteomics-how advanced are the discovery of antigens and immune modulators now? World Vaccine Congress 2004, Montreal, April 27, 2004.

Kelvin, D. Coronavirus and SARS - Biologic challenges and opportunities for vaccine development. Vaccine Congress 2004, Montreal, April 29, 2004.

Kelvin, D. Immune responses in patients with SARS: Lessons from cytokine and gene expression profiling, FACS analysis and epitope mapping. International Conference on SARS, Lubeck, Germany, May 11, 2004.

Kelvin, D. Canada-EU Thematic Research Workshop. Ottawa, June 23, 2004.

Kelvin, D. Cytokine and Gene Expression Profiling in SARS Patients. ASV-23rd Annual Meeting-Special Symposium on SARS- The 2003 SARS Outbreak: A Canadian Perspective. Montreal, July 14, 2004.

Kelvin, D. 12th International Congress of Immunology & 4th Annual Conference of FOCIS, Montreal, July 18–23, 2004.

Kelvin, D. Gene and Cytokine expression profiling in SARS. Emory University School of Medicine, Atlanta, Aug. 4, 2004.

Kelvin, D. Functional Genomics and Cohort Studies: International AIDS Vaccine Initiative (IAVI)-Vaccine Science Subcommittee Meeting. New York, August 9, 2004.

Kelvin, D. Immune response and immune pathogenesis in SARS Molecular aspects and prevention of SARS. Conference, Madrid, October 19, 2004.

Kelvin, D. Human Pathogenesis of SARS. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) – SARS Symposium, Washington, DC, November 1, 2004.

Kelvin, D. Immune Profiling in SARS Infected People. University of North Carolina Chapel Hill, North Carolina, November 4, 2004.

Kelvin, D. Overview of SARS infection and SARS vaccine development. CANVAC 4th Annual Scientific Meeting, Saint Sauveur, Montreal, November 20, 2004.

PENCE SARS 2

Blanchard, J.E., Elowe, N., Fortin, P.D., Huitema, C., Cechetto, J.D., Eltis, L.D. and Brown E.D.. High Throughput Screening of the Viral Main Protease from the Coronavirus Implicated in Severe Acute Respiratory Syndrome (SARS). Society for Biomolecular Screening. Portland, Sept. 21-25, 2003.

Blanchard, J.E., Elowe, N.H., Fortin, P.D., Huitema, C., Cechetto, J.D., Eltis, L.D. and Brown, E.D. High throughput screening identifies inhibitors of the SARS coronavirus main proteinase. International Conference on SARS one year after the (first) outbreak, Lübeck, Germany. May 8-11, 2004.

Huitema, C., Jain, R.P., Fortin, P.D., Pettersson, H.I., Zhang, J., James, M.N.G., Vederas, J.C. and Eltis, L.D. SARS 3CL protease: expression, kinetic characterization and inhibitor design. PENCE Annual General Meeting, Montréal, May 13-14, 2004.

Blanchard, J.E., Elowe, N.H., Fortin, P.D., Huitema, C., Cechetto, J.D., Eltis, L.D. and Brown, E.D. High throughput screening identifies inhibitors of the SARS coronavirus main proteinase. PENCE Annual General Meeting, Montréal, May 13-14, 2004.

Blanchard, J.E., Elowe, N.H., Fortin, P.D., Huitema, C., Cechetto, J.D., Eltis, L.D. and Brown, E.D. High throughput screening identifies inhibitors of the SARS coronavirus main proteinase. The 4th International Conference of the Canadian Proteomics Initiative, Montréal, May 14-16, 2004.

PENCE SARS 8

One invited talk at Southern Research Institute in Alabama in April 2004 and one at the SARS Accelerated Vaccine Initiative (SAVI) meeting in Vancouver in June 2004.

MITACS

Brauer F. Some simple models for disease outbreaks, International Conference on Mathematical Biology 2003, Los Alamos, June 30 - July 1, 2003.

Brauer F. A new look at some old simple disease transmission models, MITACS-PIMS Health Canada Meeting on SARS, Banff, Alberta, September 4-6, 2003.

Brauer F. Some disease outbreak models. Applied Mathematics Department, University of Washington, October 21, 2003.

Brauer F. A discrete model for SARS transmission, CMS Winter Meeting, December 6-8, 2003.

Day, T. Insights from life history theory into the evolution of infectious disease. CNRS, Montpellier, France, July 2003.

Day, T. Insights from life history theory into the evolution of infectious disease. Imperial College, Silwood Park, U.K., August 2003.

Day, T. Insights from life history theory into the evolution of infectious disease. European Society for Evolutionary Biology 9th Congress, Leeds, U.K., August 2003.

Day, T. A general theory for the evolutionary dynamics of parasite virulence. University of Edinburgh, Edinburgh, Scotland, August 2003.

Day, T. A general theory for the evolutionary dynamics of parasite virulence. University of Montpellier, Montpellier, France, Sept. 2003.

Day, T. A general theory for the evolutionary dynamics of parasite virulence. University Pierre et Marie Curie, Paris, Sept. 2003.

Gumel, A. Towards a global strategy for containing SARS. MITACS-PIMS Health Canada Meeting on SARS, September 4 -6, 2003, Banff, Alberta.

Gumel, A. Modeling SARS Outbreaks in the GTA. CAARMS9, Purdue University, June 2003.

Gumel, A. Mathematics of SARS. Distinguished Seminar Series, University of Michigan, Ann Arbor, October 2003.

Jacobson, Z. Robust Markov modeling for spreading SARS and other infectious diseases. MITACS-PIMS Health Canada Meeting on SARS, Banff, Alberta, September 4-6, 2003.

Ruan, S. Modeling Strategies for Controlling Local SARS Outbreaks. Applied Math. Seminar, University of Miami, Miami, October 3, 2003.

Ruan, S. Stability of steady states and existence of traveling waves in a vector disease model. Invited talk at the International Conference on New Directions in Dynamics of Evolution Equations, Changsha, China, December 16-20, 2003.

Ruan, S. Simulating the SARS outbreaks in Beijing. Public lecture at the Sciences & Technology University Beijing, December 15, 2003.

Ruan, S. Modeling SARS transmission. Public lecture at Hubei Institute of Education, Wuhan, December 29, 2003.

Ruan, S. Recent work on modeling SARS. Central China Normal University, Wuhan, December 31, 2003.

Ruan, S. Stability and Traveling Waves in Epidemic Models. International Conference on New Directions In Evolution Equations, Changsha, China, Dec 15-20, 2003.

Ruan, S. Traveling Waves in a Vector Disease Model. International Symposium on Dynamical Systems and Applications to Environmental and Population Systems, Hamamatsu, Japan, March 14-18, 2004.

Ruan, S. April 8, 2004, Colloquium talk on Epidemic Models at Iowa State University, Ames, USA.

Ruan, S. SARS transmission. Chinese National Conference on Mathematical Biology, Wenzhou, China, May 16, 2004.

Ruan, S. A series of lectures on the dynamics of epidemiological and biological systems. Southwestern China Normal University, Chongqing, China, May 17-22, 2004.

Ruan, S. Infectious disease models. Eastern China Normal University, Shanghai, China, May 26, 2004.

Ruan, S. Modeling Control Strategies for SARS Outbreaks. Computational and Population Dynamics, Trento, Italy, June 21-25, 2004.

Sahai, B. Lingering Issues on SARS. MITACS-PIMS Health Canada Meeting on SARS, Banff, Alberta, September 4-6, 2003

van den Driessche, P. Epidemic Thresholds. Seminar, Centre for Math Biology, University of Alberta, November 3 2003.

van den Driessche, P. The spatial spread of a multi-species disease. Math. Biol. Special Session, CMS, Simon Fraser University, December 2003.

van den Driessche, P. Contributions of mathematical modeling to controlling infectious diseases. Public Lecture, Memorial University of Newfoundland, July 8, 2004.

van den Driessche, P. Thresholds and bifurcations in some epidemic models. International Conference of Nonlinear Dynamics and Evolution Equations, St John's, Newfoundland, July 2004.

Webb, G. Critical Role of nosocomial Transmission in the Toronto SARS Outbreak. American Mathematical Society Fall Southeastern Section Meeting, October 24-25, 2003.

Watmough, J. Multiple group disease transmission models with quarantine. MITACS-PIMS Health Canada Meeting on SARS, Banff, Alberta, September 4-6, 2003.

Watmough, J. Multiple setting disease transmission models: quarantine and isolation CMS/CAIMS Joint Annual Meeting, Halifax, NS, June 2004.

Watmough, J. Disease transmission models, University of Alberta, Dec. 2003.

Watmough, J. Reproduction numbers and stability in disease transmission models, ICES/HIU data symposium, Toronto, Ontario, January 2004.

Wu, J. SARS, SAS and Math: From Public Health to Data Analysis to Mathematical Simulation. 10th Canadian Undergraduate Mathematics Conference, Toronto, May 28-June 1, 2003.

Wu, J. SARS transmission heterogeneity and control. Xi'an Jiaoton University, September 15, 2003.

Wu, J. Experience of SARS modeling in Canada. Beijing Normal University, Sept. 22, 2003.

Wu, J. MITACS Team on Infectious Diseases: History, Current Status and Future. MITACS NCE Biomedical Theme Meeting, Banff, Alberta, October 22-23, 2003.

Wu, J. Modeling Infectious Diseases: Opportunity and Challenge. 2004 MITACS annual meeting, June 2004.

Wu, J. SARS, SAS and MITACS: Mathematics for Diseases Outbreak Control and Public Health. Unionville High School, April 14, 2004.

Wu, J. Mathematical Modeling and Analysis for SARS Transmission Dynamics: Challenging, Opportunity and Relevance to Public Health management. "Studying SARS" Panel, the Bethune College/Science and Society Programme Series on Public Health in the 21st century, November 25, Toronto.

Yan, P. An overview of methods of epidemiology modeling of communicable disease outbreak. Workshop and Handbook on the Rapid Assessment of Economical Impact of Public Health Emergencies of International Concern: the Example of SARS. Organized by World Health Organization and the Canadian Public Health Association, Toronto, January 27, 2004.

Yan, P. Introduction to SPECTRUM with Emphasis on Submodule AIM: a software developed by UNAIDS and the Futures Group International for Projecting the Demographic Impact of HIV/AIDS. 2004 National HIV/AIDS Surveillance and Testing Conference and Workshop of China, Nanchang, China, February 28, 2004.

Yan, P. Statistical Concepts Adopted to Clinical Trials, with Extended Discussions to Vaccine Trials. International Workshop on Development of Vaccines for SARS and Bird Flu. Organized by World Health Organization and Ministry of Science and Technology of China, Beijing, China, March 1, 2004.

Yan, P. Super-spreading Events. Their Implications on Transmission Potential, Epidemic Control Measures and Interpretation of Trends. Institute of Applied Mathematics, Chinese Academy of Science. Beijing, China, March 6, 2004.

Yan, P. On Biases in HIV Prevalence Estimates. UNAIDS Reference Group Meeting, Montreux, Switzerland, May 10, 2004.

Yan, P. Heterogeneous Transmission of Infectious Diseases: Implications on Transmission Potential, Epidemic Control Efforts and Interpretation of Trends. 2004 Hawaii International Conference on Statistics, Mathematics and Related Fields, Honolulu, Hawaii, June 11, 2004.

Yan, P. Heterogeneous Transmission: Implications on Transmission Potential, Control Efforts and Trend Interpretation. PIMS-MATICS-MSRI Special Program on Infectious Disease, Banff, Alberta, June 28, 2004.

Yan, P. Time-series of SARS by time of infection and their usefulness in modelling, a back-calculation approach. MITACS-PIMS Health Canada Meeting on SARS, Banff, Alberta, September 4-6, 2003.

Zeng, Q. Impact of Health-Care Setting and Social Network on SARS Transmission Dynamics. MITACS NCE Biomedical Theme Meeting, Banff, Alberta, October 22 - 23, 2003.

Zhou, Y. SARS prediction in China. CMS 2004 annual meeting, Halifax, June 2004.

Zhu, H. Critical roles of health care settings in the nonsocomical transmission of SARS. MITACS-PIMS Health Canada Meeting on SARS, Banff, Alberta, September 4-6, 2003.

Zhu, H. Critical roles of health care settings in the nonsocomical transmission of SARS. York Industrial and Applied Math. Seminar, September 18, 2003.

APPENDIX 11:

MEDIA COVERAGE

CIHR Institute of Infection and Immunity

Dr. Bhagirath Singh

London Free Press, SARS, March 18, 2003
New PL, SARS, March 25, 2003
National Post, SARS, March 25, 2003
6X FM (Fanshawe College), SARS, March 26, 2003
CBC Newsworld-Calgary, SARS, March 26, 2003
CBC Radio, March 26, 2003
CBC Radio (syndication), SARS, March 26, 2003
CBC Radio, SARS, March 26, 2003
Simcoe Reformer, SARS, March 26, 2003
Rogers, SARS, March 26, 2003
CBC Radio, SARS, March 26, 2003
CHRW, SARS, March 26, 2003
Macleans, SARS, March 26, 2003
Toronto Star, SARS, March 26 and 27, 2003
Ottawa Citizen, SARS, March 27, 2003
AM 96 (local radio-CORUS), SARS, March 28, 2003
The Londoner, SARS, March 31, 2003
New PL, SARS, March 31, 2003
London this Week, SARS, March 31, 2003
CHUM Radio, SARS, April 1, 2003
CKNW AM 980 (Corus-Vancouver), SARS, April 1, 2003
London Free Press, SARS, April 1, 2003
CBC Radio Windsor, SARS, April 2, 2003
CBC Radio Toronto, SARS, April 2, 2003
6X FM, SARS, SARS, April 3, 2003
Global TV, SARS, April 3, 2003
CBC News On-line, SARS, April 3, 2003
Star Phoenix (Saskatoon), SARS, April 3, 2003
National Post, SARS, April 3, 2003
Toronto Star and European specialty medical newspaper, SARS, April 3, 2003
CBC Newsworld (Calgary), SARS, April 4, 2003
Globe and Mail, SARS, April 4, 2003
CTV Newsnet, SARS, April 8, 2003
London Free Press, SARS, April 9, 2003
Time Magazine, SARS prevention, timeline for control, April 10, 2003
London Free Press, SARS RFP, April 10, 2003
Report on Business TV, SARS, April 10, 2003
Science's Next Wave (Science Magazine), SARS research funding, April 10, 2003
Miami Herald, SARS-why no deaths in US, April 10, 2003

6X FM News, SARS, April 11, 2003
CBC Radio (French), SARS genome, April 14, 2003
Radio Canada International, SARS genome, April 14, 2003
CHUM (Windsor), SARS genome, April 14, 2003
CBC Radio-The Current, SARS-future, April 14, 2003
Toronto Star, SARS-public health/research capacity, April 15, 2003
The Daily Princetonian, SARS, April 16, 2003
Canadian Press, SARS, April 17, 2003
CBC Newsworld (Calgary), SARS control-logistics, April 21, 2003
Bloomberg News, Appropriate use of quarantines-voluntary *vs* legal, April 21, 2003
National Public Radio (US), Ont. Preparedness, April 21, 2003
Toronto Sun, SARS compared to other diseases, April 22, 2003
Toronto Star, SARS-how does a normal person protect themselves?, April 23, 2003
1290 CJBK (London), SARS-WHO advisory, April 23, 2003
National Post, SARS-funding for vaccine research, April 24, 2003
Canadian Press, April 25, 2003
Radio Canada, SARS effect on research, April 25, 2003
Radio Canada Intl. (Business Sense), SARS research, April 28, 2003
CTV Newsnet, Infrared scanners and SARS, April 28, 2003
CBC Radio (French), April 29, 2003
CBC Radio (Vancouver), BC government announced funding for SARS, April 29, 2003
Radio-Canada International, Canada's health system/expert opinion on SARS, April 29, 2003
Le Soleil (Quebec City), SARS RFP, April 29, 2003
London Free Press, Minister's comment on CDC-like center in Canada, May 5, 2003
CBC Radio (Vancouver), Thermal scanners at airports, May 6, 2003
CBC Newsworld, SARS-new cases, May 8, 2003
Radio Canada International, SARS, May 26, 2003
CTV national news, SARS, May 26, 2003
Reuters, SARS, June 11, 2003
Science Magazine, SARS consortium, June 13, 2003
Reuters, SARS, July 2, 2003
CBC, CIHR/SARS, July 25, 2003
CTV, CIHR/SARS, July 25, 2003
Canadian Press, CIHR/SARS, July 25, 2003
CBC, CIHR/SARS, July 25, 2003
CFRB News talk 1010, CIHR/SARS, July 25, 2003
Media Inc., CIHR/SARS, July 25, 2003
Globe and Mail, CIHR/SARS, July 25, 2003
Fairchild TV, CIHR/SARS, July 25, 2003
CFTO, CIHR/SARS, July 25, 2003
OMNI TV, CIHR/SARS, July 25, 2003
Toronto Sun, CIHR/SARS, July 25, 2003
CBC National Radio News (Syndication), SARS, July 30, 2003
The Wall Street Journal, SARS, CSRC, HC and Frank Plummer, August 22, 2003
Canadian Healthcare Manager Magazine, SARS, March 1, 2004
CJBK radio, SARS, March 5, 2004

SAVI

There has been extensive media interest in this research initiative, but this has not been systematically tracked. The citations below are a representative sample only.

Dr. Skowronski

National Post: The battle of the bugs: a vaccine would be the best defense against SARS. January 17, 2004
++ TV, radio – CBC, Global, CTV national and local (didn't keep track)

Dr. Babak Pourbohloul/Dr. Lauren Meyers

BBC, Wired.com, The World, Newsweek, Die Zeit, Local NBC TV, KXAN 36 (related to novel application of network theory to modeling of spread of infectious diseases)

Dr. Lorne Babiuk

CBC TV and radio national (vaccine trials, cattle vaccine). May 6, 2004
CBKF-FM (Regina), CHQR-AM (Calgary), CKRM-AM (Regina), CBKFT-TV (Sask), Global TV (Sask), CTV-SK, CTV (Canada AM) May 6-8, 2004 (related to SARS vaccine development).

Dr. David Patrick

Globe & Mail, National Post, local and national TV/radio – related to application of diagnostic tests to a pseudo-SARS outbreak at a long term care facility in Surrey, British Columbia in August, 2003.

Dr. Martin Petric

Vancouver SUN spring 2004 (related to SARS vaccine development)

MITACS (SEE MORE IN MITACS HOMEPAGE)

Infectious Diseases Workshop, July 2004:

Dr. Jianhong Wu and Dr. Fred Brauer, Ottawa Citizen, July 6, 2004.
Dr. Wu and Dr. Brauer, Edmonton Journal, July 6, 2004.
Dr. Wu and Dr. Brauer, Calgary Herald, July 6, 2004.
Dr. Troy Day, CHQR/QR77 Radio in Calgary, July 5, 2004.

APPENDIX 12:

MEMBERS OF THE CANADIAN RAPID RESEARCH RESPONSE TEAM AS OF SEPTEMBER 2004

Organization	Name	Position
Canadian Food Inspection Agency (CFIA)	Judith Bossé	Vice-President, Science
Canadian Institutes of Health Research (CIHR)	Alan Bernstein	President
CIHR Institute of Health Services and Policy Research	Morris Barer	Scientific Director
CIHR Institute of Infection and Immunity	Lorne Babiuk	Chair, Institute Advisory Board
CIHR Institute of Infection and Immunity	Bhagirath Singh (Chair)	Scientific Director
CIHR Institute of Population and Public Health	John Frank	Scientific Director
Centers for Disease Control and Prevention (CDC)	To be determined	Director
Chief Medical Officer of Health	James Talbot	A/Chief Medical Officer of Health
National Institutes of Health (NIH)	To be determined	Deputy Director
Private Sector Rx&D	Jean Marion	Director, Scientific Affairs
Provincial Health Research Agency	Aubrey Tingle	President
Public Health Agency of Canada and Health Canada	Frank Plummer	Acting Chief Public Health Officer, Scientific Director
WHO	To be determined	Coordinator, Global Alert & Response, CDS/CSR/GAR

APPENDIX 13:

EVALUATION OF THE RELEVANCE, SUCCESS AND EFFICIENCY OF THE CSRC – EXECUTIVE SUMMARY

CONTEXT

The Canadian SARS Research Consortium (CSRC) was created in June 2003 to ensure that Canada's health research community, funding agencies and industry were able to mount a rapid and effective research effort in response to SARS. The aims of the evaluation of the CSRC were to determine its overall effectiveness, efficiency and relevance and to provide the Consortium with recommendations on how the performance of this model could be improved.

METHODS

The main source of evaluation information was 25 key-informant interviews with 27 participants and stakeholders in the CSRC initiative. Interviewees included representatives of the CSRC Management Group, CSRC Scientific Advisory Committee, successful and unsuccessful researchers in the SARS I and SARS II research competitions and other stakeholders, including Canadian and international researchers involved in relevant areas, SARS I and SARS II peer review committee members and CIHR institute and corporate senior managers.

MAIN FINDINGS AND LESSONS LEARNED

Views of the stakeholder community on the effectiveness of the CSRC varied, with most seeing it as a qualified success. There was wide agreement that many valuable lessons have been learned through the SARS experience and the CSRC experiment and that these should be applied in building an ongoing research response capacity for future emerging health threats.

Lessons learned

1. **The Canadian research community is willing and able to mobilize**, to work in partnership and collaboration across sectors and institutions, putting personal and organizational interests aside in the interest of responding to a health crisis, and to innovate in finding new ways of working together so as to respond more quickly and effectively.

2. **There is a need to create a permanent national coordination entity to coordinate a rapid research response** to emerging infectious diseases. This entity should proactively develop mechanisms for:

Structural issues

- **Flexible contingency funding,** so that adequate funds can be immediately accessible. This will ensure that the research community's attention is entirely focused on the research issues and not on where the money will come from and that hard choices about siphoning resources from other existing priorities do not have to be made in the context of a crisis.

- **Overcoming organizational barriers to formal partnerships.** The legal and liability issues involved in the CSRC partnership model should be examined and resolved, resulting in generic templates that can be adapted expeditiously when needed.

- **Creating mechanisms of effective international collaboration.** The relationships and processes required to ensure effective information sharing and facilitation of collaborative international research efforts (for example, through exchange of patient materials, epidemiological data, etc.) should be put in place prior to a next emerging crisis.

- **Creating an inventory of expertise.** Creation and maintenance of a national inventory of relevant research expertise in areas of likely future health threats could expedite the mobilization of the research community and the mounting of coordinated research efforts in the face of emerging threats. Effective collaboration among researchers in different parts of the country could be enhanced if members of the inventory also had opportunities to interact and build trust and goodwill prior to a crisis situation.

- **Considering alternatives to the standard open competition funding model**, for example by directly targeting funds to teams with known capacity and expertise. The advantages and risks of such models should be considered and debated outside the crisis situation.

Research facilitation issues

- **Rapid and appropriate peer review.** Concerns raised about the appropriate composition of peer review committees should be addressed, perhaps through the creation of a roster of potential peer reviewers with a wide range of expertise willing to be part of an emergency peer review process if needed.

- **Expedited and effective ethics review for research conducted in the path of an ongoing outbreak**. Proactive, anticipatory attention to ethical issues and their review is required to ensure that patient safety remains paramount, that standards are consistent, and that procedures do not cause loss of precious time.

- **Coordination of access to patient specimens.** The importance and complexity of this issue became apparent during the SARS outbreak, as the lack of coordination probably contributed to some inefficiencies in the research effort. Establishment of mechanisms and protocols for sample coordination prior to outbreaks would prevent this and the resulting tensions that arise.

- **Protocols for the conduct of clinical trials in an ongoing outbreak or epidemic.** Having protocols in place and ensuring adequate communication among sites involved in clinical trials would address the difficulties encountered in the SARS outbreak. Mechanisms could also be developed for facilitating the participation of researcher/clinicians most directly involved in managing the outbreak, in research during the outbreak itself.