

Vaccines for the 21st Century

Taking Canada to the Next Level



CIHR IRSC

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infectieuses et immunitaires

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Report prepared for
CIHR Institute of Infection and Immunity
by
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List of Abbreviations

| | |
|----------|--|
| BCG | bacillus Calmette-Guérin |
| BSL 3 | biosafety level 3 |
| CAIRE | Canadian Association of Immunization Research and Evaluation |
| CDC | Centers for Disease Control and Prevention |
| CFIA | Canadian Food Inspection Agency |
| CHVI | Canadian HIV Vaccine Initiative |
| CIC | Canadian Immunization Committee |
| CIDA | Canadian International Development Agency |
| CIHR | Canadian Institutes of Health Research |
| CIHR-III | CIHR Institute of Infection and Immunity |
| CIH2 | Canadian International Immunization Initiative Phase 2 |
| CIN | cervical intraepithelial neoplasia |
| CPS | Canadian Pediatric Society |
| CTA | cancer-testis antigen |
| CTL | cytotoxic lymphocyte |
| DRDC | Defense Research and Development Canada |
| FDA | Federal Drug Administration |
| FRSQ | Fonds de la recherche en santé du Québec |
| HC | Health Canada |
| HCV | hepatitis C virus |
| HDP | host defense peptides |
| HIV | human immunodeficiency virus |
| HPV | human papilloma virus |
| HSV | herpes simplex virus |
| IAB | Institute Advisory Board |
| IDRC | International Development Research Centre |
| IMPACT | Immunization Monitoring Program, Active |
| GHRI | Global Health Research Initiative |
| GMP | good manufacturing practices |
| LD | lethal dose |
| LPS | lipopolysaccharide |
| NACI | National Advisory Committee on Immunization |
| NCIC | National Cancer Institute of Canada |

| | |
|---------|---|
| MHC | major histocompatibility complex |
| MRSA | methicillin-resistant <i>Staphylococcus aureus</i> |
| NK | natural killer |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| NRC | National Research Council Canada |
| NSERC | Natural Sciences and Engineering Research Council |
| OHASIS | Occupational Health And Safety Information System |
| PHAC | Public Health Agency of Canada |
| PIV3 | human parainfluenza virus type 3 |
| PREVENT | Pan-Provincial Vaccine Enterprise |
| RSV | respiratory syncytial virus |
| RI | retro-inversed |
| SARS | Severe Acute Respiratory Syndrome |
| TB | tuberculosis |
| TLR | Toll-like receptor |
| UBC | University of British Columbia |
| UNICEF | United Nations Children’s Fund |
| UIIP | universal influenza immunization program |
| VIC | Vaccine Industry Committee |
| VIDO | Vaccine and Infectious Disease Organization |
| WHO | World Health Organization |



Executive Summary

About this report

In its Strategic Plan for 2007-2012, the Canadian Institutes of Health Research (CIHR) Institute of Infection and Immunity (CIHR-III) made Vaccines of the 21st Century a research priority. The Institute surveyed representatives from vaccine-related organizations, individual researchers and representatives from funding organizations. They were asked to:

- Summarize their accomplishments and/or investments in research;
- Identify challenges; and
- Make suggestions for facilitating and supporting research and translating knowledge into new products and services.

Their responses form the basis of this report and will guide the activities of this strategic priority area for the Institute.

The broad nature of this report, however, also makes it useful for government policy makers, those who support research and development, members of the research community and “end users” of vaccines such as health-care professionals and governments.

The time is right

The Vaccines of the 21st Century strategic research priority is well-timed. Renewed interest in research and development is being driven by several converging factors including:

- A lack of new antibiotics to fight infections;
- A dearth of vaccines for several major diseases;
- Threats from emerging infectious diseases, pandemic influenza and bioterrorism;

- New uses for vaccines (e.g. to prevent and to treat cancer);
- Renewed interest in global health; and
- A need to maintain national capacity to develop, manufacture and test vaccines.

Basic research to vaccination

From basic research to the implementation of immunization programs, a number of organizations engage in vaccine-related activities. Canadian universities, research institutes, governments and vaccine companies do basic research. Clinical trials are conducted by vaccine manufacturers and at vaccine evaluation centres. Others play a role in vaccine approval and make recommendations to health-care professionals and governments.

Strong track record

Canada has a history of making significant contributions to vaccine research and development. Accomplishments over the past decade include:

- Developing an acellular pertussis vaccine from basic research to manufacture by sanofi pasteur;
- Developing vaccine technology to prevent meningitis by Dr. Howard Jennings at the National Research Council of Canada;
- Preparing for and assessing the impact of human papilloma virus (HPV) immunization in Canada by Dr. Babak Pourbohouh at the BC Centre for Disease Control, Dr. Marc Brisson at Laval University and Dr. Eduardo Franco at McGill University;
- Assessing and making recommendations for influenza

immunization programs by Dr. Noni Macdonald at the Canadian Centre for Vaccinology, Dalhousie University and Dr. Jeff Kwong at the Institute for Clinical Evaluative Sciences;

- Developing a vaccine candidate for Severe Acute Respiratory Syndrome (SARS) by the SARS Accelerated Vaccine Initiative led by Dr. Brett Finlay and Dr. Robert Brunham at the University of British Columbia (UBC) Centre for Disease Control;
- Developing and licensing a cattle vaccine against *E. coli* O157:H7 by Dr. Andrew Potter at the Vaccine and Infectious Disease Organization (VIDO) and Dr. Brett Finlay at the UBC Centre for Disease Control;
- Developing candidate vaccines against hemorrhagic fevers by Dr. Heinz Feldmann and Dr. Steven Jones at the Public Health Agency of Canada (PHAC) National Microbiology Laboratories;
- Researching and developing adjuvants, which are added to vaccines to enhance immune responses, by GlaxoSmithKline Inc. and several individual researchers at universities; and

- Developing therapeutic cancer vaccines by manufacturers and researchers at universities including Dr. Jonathan Bramson at McMaster University.

The research accomplishments described by representatives of vaccine-related organizations and individual researchers highlight specific research strengths in Canada. There is strength in research into novel adjuvants and methods of antigen delivery, as well as determining how to evoke specific types of immune responses. Epidemiology, vaccines for special populations and evaluation research are also strong areas. Over 25 different infectious agents are under study with the most common being influenza, therapeutic cancer vaccines, HPV and human immunodeficiency virus (HIV).

Challenges and recommendations

Survey respondents identified challenges and made suggestions on how CIHR and partners can facilitate vaccine research and development. These include:

| Challenges | Recommendations |
|---|--|
| Research efforts need to be better coordinated. | Organize and facilitate vaccine research workshops and facilitate communication. Foster linkages between all stakeholders. Establish a vaccine research network. |
| Vaccine research and development is costly. | Create partnerships with funding organizations, industry, academic institutions and government to drive research and development. |
| There are still several major diseases for which there currently are no vaccines. As well, improved methods to formulate and deliver vaccines are needed. | Continue to support basic research. Also, develop and support strategic research initiatives. |
| The public lacks accurate knowledge about the safety and efficacy of vaccines. | Support behavioural, social and ethics research. |

| Challenges continued | Recommendations continued |
|---|---|
| There is a gap between basic research and Phase I/II clinical trials. | Partner with industry to bridge the gap between basic science and clinical trials. Establish facilities and guidelines to allow researchers to take discoveries towards clinical trials. Create new funding mechanisms. |
| There are many clinical research questions that require public funding. | Provide additional and ongoing support for pre-clinical and post-licensure trials. |

| Additional challenges not specifically related to research |
|--|
| Up-to-date and standardized data on the epidemiology and burden of disease is often lacking. |
| It is increasingly difficult for industry to do clinical trials in Canada. |
| Industry needs faster and more transparent vaccine approval. |
| Canada must retain and develop its own vaccine production facilities. |
| Immunization programs across the country need to be harmonized. |
| Additional recommendations not specifically related to a challenge |
| Improve the grant application process, review and approval times. |
| Train more vaccinologists and develop additional scientific and regulatory expertise. |

Funding and Recent Announcements

Vaccine-related research is funded by several agencies and organizations operating at provincial, national and international levels. Several new funding opportunities for vaccine research were identified by representatives from funding organizations. These include the Influenza Research Network launched by PHAC and CIHR-III and the Canadian HIV Vaccine Initiative.

In addition, several exciting announcements regarding vaccine research and development were made in early 2008. For example, a new Centre of Excellence for Commercialization

and Research called The Pan-Provincial Vaccine Enterprise (PREVENT) will conduct pre-clinical and proof-of-concept clinical trials for promising early-stage vaccine candidates. A Canadian Network on HPV Prevention, operated by the International Centre for Infectious Diseases, is also in development. As well, the Alberta Heritage Foundation for Medical Research (AHFMR) has awarded an Interdisciplinary Team Grant in Vaccine Design and Implementation to study how bacteria evolve within the human population and design vaccine products to protect against different strains and species.

Conclusion

Canada continues to make significant contributions to vaccine research and development. These accomplishments have saved lives, decreased human suffering and reduced health-care costs. Exciting new funding initiatives and a renewed interest in vaccines combine to make this an ideal time for CIHR-III to launch its strategic research priority. The new-found enthusiasm must be maintained, however, and many individuals, organizations and countries will have to work together to succeed.

Next steps

CIHR-III will use this report – which will be distributed to stakeholders in vaccine research and development and immunization – to develop an action plan and build partnerships for the Vaccines of the 21st Century strategic priority. The goals of the priority are to help to coordinate research efforts, foster linkages, facilitate vaccine research and development and support the transfer of research knowledge to governments, health-care providers and the public.

These activities will take vaccine research and development in Canada to the next level, and ultimately, improve health and well-being in Canada and around the world.

About This Report

The purpose of this report is to help CIHR-III plan a strategic initiative for Vaccines of the 21st Century, one of five priorities in its Strategic Plan for 2007-2012. The broad nature of this report, however, also makes it useful for policy makers, organizations that support research and development, members of the vaccine research community and all who are interested in and benefit from vaccines and immunization programs.

This report provides an overview of vaccine-related research and development in Canada, and is based on surveys of researchers and representatives from vaccine-related organizations and funding agencies. The

strength of Canadian research is showcased in a summary of research activities and recent accomplishments. Current challenges in vaccine research and development and in immunization are discussed, along with recommendations on how these can be addressed and overcome. Recent and anticipated investments in research by funding agencies are also summarized. The background section provides an overview of vaccines, the steps in vaccine research and development and reasons for the renewed interest in vaccines.





Background

Vaccines Overview

Over the past century, vaccination has saved more lives than any other health-care intervention. Its effectiveness and low cost have made it essential to maintaining public health. Smallpox has been eradicated, and the suffering and death caused by over 30 other infectious diseases, including typhoid, diphtheria, polio, measles, mumps, rubella, hepatitis A, hepatitis B, pneumococcus, meningococcal disease and tetanus has been drastically reduced.

A vaccination stimulates the immune system with a particular agent (e.g. bacterium, virus, toxin) causing it to develop immunological memory. Anything that stimulates an immune response, whether naturally or via vaccination is called an antigen. Vaccinated individuals produce a much stronger immune response if they encounter the agent again and will have a much lower chance, if any, of developing disease.

There are two main types of immune responses: cell-mediated, in which specific cells called cytotoxic T cells attack cells in the body that have become infected, and humoral, in which the body develops antibodies that neutralize and help eliminate antigens in the blood, on epithelial surfaces and in the fluid that bathes tissues.

Several classes of vaccines exist. In some cases, bacteria or viruses are heat-inactivated or killed with chemicals (inactivated vaccines) or grown in cell culture (attenuated vaccines) in order to disable their virulent properties. In other cases, only the toxin produced by a bacterium or a protein portion of an agent (subunit vaccines) is used in the

vaccine. Sometimes a subunit is attached to a toxin (conjugate vaccines) in order to evoke a stronger immune response. Vaccines usually contain adjuvants such as aluminum salts or oil and water emulsions. These enhance the immune response or elicit a specific type of immune response, either cell-mediated or humoral. Newer approaches use DNA or RNA coding for a component of the agent in the vaccine. The DNA or RNA can be transferred using a viral vector in which a non-pathogenic form of a virus is used.

Vaccines are generally administered via injection or are taken orally, and sometimes boosters are needed to develop and maintain immunological memory. Vaccines can be preventative (prevent occurrence of disease) or therapeutic (administered after infection or disease onset to enhance natural immunity).

Steps in Vaccine Research and Development

Vaccine research and development is a continuum from basic research to clinical trials (Figure 1). The research begins with the identification of an infectious agent or disease. Methods to detect the agent are needed to understand the causes and transmission of the disease and for subsequent clinical vaccine trials. An understanding of the agent's biology and how it infects and causes pathogenesis is useful in identifying candidate antigens. In addition, understanding the types of immune responses that confer protection against infection is useful for formulating an effective vaccine and for subsequent clinical vaccine trials.

Once antigens have been chosen, methods to formulate and deliver the vaccine are developed and tested in animal models. Vaccines produced for human trials must be manufactured according to good manufacturing practices (GMP). Human clinical testing involves four phases. Phase I trials examine safety of the vaccine in a small number (20-100) of healthy individuals. Phase II trials examine safety and immunogenicity (the ability to stimulate the immune system) in a larger number of individuals (100-300). In Phase III trials, the

vaccine is administered to many individuals (2,000-10,000) and information about safety and immunogenicity is gathered. If the candidate vaccine is deemed effective in Phase III clinical trials, then an application for licensure is submitted to regulatory bodies such as Health Canada (HC) and the Federal Drug Administration (FDA). Post-licensure trials (i.e. vaccine evaluation) are often performed to assess long-term vaccine effectiveness, as well as the health, social and economic effects of the vaccine.

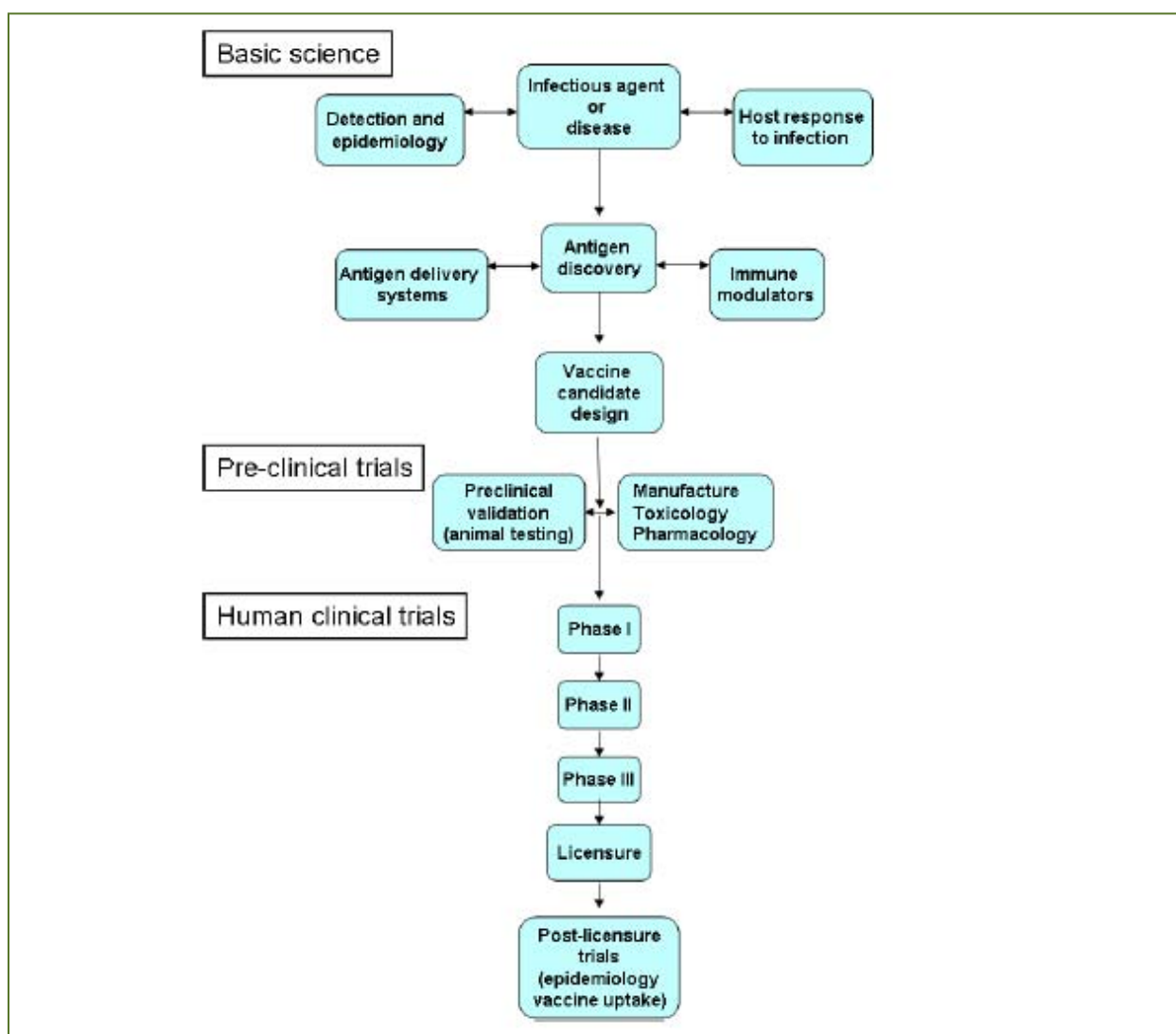


Figure 1: The vaccine research and development continuum. Modified from figures from: <http://www.savi-info.ca/Vaccine.htm> and <http://www.cihr-irsc.gc.ca/e/34251.html>

Reasons for Renewed Interest and the Need to Support Vaccine Research

Only five multinational companies currently develop and manufacture most of the vaccines used today, down from the approximately 30 companies that existed about 35 years ago. The decline stems from the introduction of GMP for vaccine production in the 1980s, which substantially increased production costs, and traditionally low profit margins because governments are bulk purchasers of vaccines. The threat of liability lawsuits has also played a role. Interest in vaccines, however, has been renewed over the past few years for the following reasons:

Antibiotic resistance and lack of new antibiotics

Microorganisms including bacteria develop resistance to antibiotics over time. Over the past five to ten years, there has been a decline in the development and approval of new antibiotics. Alternatives for antibiotics, such as vaccines, are urgently needed.

There are several major infectious diseases for which vaccines are still needed

There are no vaccines for several major infectious diseases, including HIV, hepatitis C and malaria. These diseases have devastating effects on health, the economy and society. Vaccines would be an effective and relatively low-cost method to combat these diseases.

Emerging infectious diseases and potential threats such as pandemic influenza

The emergence of SARS and its rapid spread between countries via global travel heightened awareness of the potential threat of emerging diseases. In addition,

many experts agree that the next influenza pandemic is overdue, and recent human deaths caused by a highly pathogenic strain of avian influenza have intensified concerns.

Bioterrorism threat

Increased concern over potential bioterrorism attacks has led to renewed government support for research and the development of methods to counter biological agents that threaten national security and public safety.

Newer uses for vaccines

Vaccines are now being developed and marketed to prevent and treat cancer. Preventative vaccines include vaccines against hepatitis B to prevent liver cancer and vaccines against HPV to prevent cervical cancer. Many therapeutic cancer vaccines are being developed, including one for the treatment of kidney cancer that received Russian approval in April 2008. These vaccines have opened a new avenue for research and development.

Renewed interest in global health

Private philanthropic organizations such as the Bill and Melinda Gates Foundation have targeted malaria, tuberculosis, HIV and other vaccine-preventable and infectious diseases for investment. As a result, more researchers have made these areas a focus of their research.

Need to maintain capacity to develop, manufacture and test vaccines in Canada

Given the potential threats and opportunities for new vaccine therapies, there is a renewed drive for Canada to maintain and enhance capacity to develop, manufacture and test vaccines in order to optimally protect and treat its citizens.

Data Collection Methods

This report was researched and written by Dr. Michelle French, Scientific Communication. Information was gathered in three phases. In the first phase, over 20 phone interviews were conducted with key representatives from vaccine-related organizations with a broad range of expertise (Appendix 1). See Appendix 2 for the interview questions. In the second phase, approximately 240 researchers engaged in vaccine-related research were asked via e-mail to complete a web-based survey (see Appendix 3 for survey questions). For the final stage, over 40 representatives from funding agencies (Appendix 4) were contacted via e-mail and asked to complete a questionnaire (Appendix 5). All questions and lists were prepared in consultation with the CIHR-III Advisory Board Sub-Committee on Vaccines of the 21st Century (IAB Sub-Committee, Appendix 6).

A draft of this report was circulated to all individuals who were originally contacted. Errors and omissions that were identified were corrected in the final version. While attempts were made to collect data from as many organizations and researchers as possible, some research and information will have been omitted because researchers declined to participate or could not be contacted via e-mail. The report contains as many comments and suggestions as possible from those who participated.

The report includes vaccine and related immunization research programs, but excludes immunotherapy such as passive immunization with antibodies.

The views expressed herein do not necessarily represent those of all respondents, CIHR-III, or the report writer (Michelle French). Most of the data was collected by the end of February 2008.

Survey Results

Vaccine-Related Organizations in Canada

There are a number of organizations in Canada that are engaged in vaccine-related activities from basic research through to the implementation and evaluation of immunization programs. See Table 1 for a list of the organizations and their main vaccine-related activities. Further details including the current activities of each organization and their international linkages are described in Appendix 7. Information for this section came from responses by representatives of vaccine-related organizations who were asked to briefly describe the vaccine-related research programs of their organization.

Basic research (e.g. microbiology, immunology, vaccinology) is conducted at universities and research institutes, government organizations and in the private sector. Clinical trials are conducted by vaccine manufacturers and by teams at vaccine evaluation centres in Vancouver, Montreal, Quebec City and Halifax. Once vaccines have been approved for use, organizations such as the National Advisory Committee on Immunization (NACI) make recommendations to provinces and health-care workers regarding immunization programs and protocols. Most of the research performed at universities and research institutes is included elsewhere in this report (see “Selected key accomplishments”).

Table 1: Vaccine and immunization organizations in Canada and their vaccine-related activities

| Organization | Vaccine-related activities |
|--|---|
| BIOTECCanada | Consists of representatives from small and medium size enterprises (biotech) and core multinational companies, including vaccine developers and producers. Represents industry to government. |
| Canadian Association of Immunization Research and Evaluation (CAIRE) | An association of over 100 vaccine-orientated researchers. Many engaged in evaluating new vaccines, building the rationale for new public programs and optimizing public immunization programs. |
| Canadian Centre for Vaccinology/Clinical Trials Research Center | Includes scientists and experts in diverse fields who conduct research programs to develop, evaluate and generate new vaccines and vaccine technologies. |
| Canadian Coalition for Immunization Awareness and Promotion | A partnership of national non-governmental, professional, health, consumer, government and private sector organizations with a specific interest in promoting the understanding and use of vaccines amongst health-care providers and the public. |

| Organization continued | Vaccine-related activities continued |
|---|---|
| Canadian Food Inspection Agency (CFIA) | Dedicated to safeguarding food, animals and plants in Canada. This includes supporting vaccine research and animal vaccination, which prevents the spread of disease to humans. |
| Canadian HIV Vaccine Initiative (CHVI) | A partnership between the Canadian International Development Agency (CIDA), PHAC, Industry Canada, CIHR and Health Canada (HC) with the goal to develop a safe, effective, affordable and globally accessible HIV vaccine. Canada's contribution to the Global HIV Vaccine Enterprise. |
| Canadian HIV Trials Network (CTN) | A partnership of clinical investigators, physicians, nurses, people living with HIV/AIDS, pharmaceutical manufacturers and others that facilitate HIV/AIDS clinical trials including vaccine trials. |
| Canadian Immunization Committee (CIC) | A group of provincial, territorial and federal immunization organizations that guide the implementation of a national immunization strategy. |
| Canadian Pediatric Society | An association of pediatricians involved in professional and public education, advocacy, surveillance and research. Monitors infectious diseases in children that are vaccine preventable and records adverse events following immunization. |
| Centre for Immunization and Respiratory Infectious Diseases, PHAC | Collaborates with the provinces and territories, other federal departments, and others to prevent, reduce or eliminate vaccine-preventable and infectious respiratory diseases; reduce the negative impact of respiratory infections; and maintain public and professional confidence in immunization programs. |
| Defence Research and Development Canada, Department of National Defense | Performs research and develops technology for national security. Includes research on and acquisition of vaccines against organisms that could be used in biological warfare. |
| GlaxoSmithKline Inc. | A global pharmaceutical company involved in vaccine research, development and manufacture in Canada. This includes clinical research on new vaccine products and epidemiological research on the burden of disease. Canada's annual influenza vaccine supplier. |

| Organization continued | Vaccine-related activities continued |
|---|---|
| McMaster Centre for Gene Therapeutics | Conducts research and develops gene- and cell-based vaccines for therapeutic intervention in cancer and infectious diseases. Primary interest in vaccines to provide mucosal immunity. Established in 1998, provides the infrastructure for cell-based cancer vaccine trials in Canada. |
| Merck Frosst Canada Ltd | A global pharmaceutical company involved in vaccine research, development and manufacture. In Canada, performs clinical trials (mostly Phase III, some Phase I/II). Committed to working with academic and clinical researchers in collaborative projects concerning vaccine-preventable diseases in order to assist Canadian decision makers (i.e. epidemiologic research, outcomes research). |
| National Advisory Committee on Immunization (NACI) | Consists of recognized experts in the fields of pediatrics, infectious diseases, immunology, medical microbiology, internal medicine and public health. Makes recommendations for the use of vaccines currently or newly approved for use in humans in Canada. |
| National Research Council of Canada (NRC) Institute for Biological Sciences | Engaged in research focused on infectious diseases, cancer vaccines, immunotherapeutics and neurodegenerative diseases. About 60% of the research is directed towards discovery of new vaccine strategies. |
| PHAC National Microbiology Laboratory | Performs reference microbiology and surveillance, support to epidemiology programs and conducts applied and discovery research including research for vaccines against pathogenic viruses and bacteria. |
| sanofi pasteur | A global pharmaceutical company involved in vaccine research, development and manufacture. In Canada, conducts basic research, epidemiological studies and clinical trials. Also, develops and manufactures vaccines. |
| UBC Centre for Disease Control | Performs vaccine research from antigen discovery to pre-clinical studies, as well as the evaluation of the impact of vaccines. |
| Vaccine and Infectious Disease Organization (VIDO) | Conducts research and develops vaccine and immunity enhancing technologies for humans and animals. Works to ensure that discoveries are commercialized. |

| Organization continued | Vaccine-related activities continued |
|---|---|
| Vaccine Evaluation Centre, BC Children’s Hospital | Conducts research to determine vaccine safety and effectiveness; evaluates new vaccines; studies vaccine preventable infections and enhances public immunization programs. Was established in 1988, making it the first formal centre for independent vaccine research in Canada. |
| Vaccine Industry Committee (VIC) | A sub-committee of BIOTEC Canada consisting of industry representatives with a focus to create a vaccine environment conducive to the goals of public health and manufacturers. |
| Wyeth Canada | Wyeth is a global pharmaceutical company that is involved in vaccine research, development and manufacture. Wyeth Canada performs Phase I-III clinical trials. |

Selected Key Accomplishments

Canadian researchers working in universities, research institutes, government organizations, industry and clinical settings have made many significant contributions to the field of vaccine research and development. The information for this section was selected from responses made by representatives from vaccine-related organizations and individual researchers.

Representatives from vaccine-related organizations were asked:

- What are the major accomplishments that your organization has made in the area of vaccines and immunization programs over the past five years?
- What are the anticipated or realized impacts of the research accomplishments of your organization?

Individual researchers were asked to:

- Summarize your top one to three research projects/accomplishments from the past five years.

Selected key accomplishments are described below. See Appendix 8 for a summary of all

key accomplishments described by representatives from vaccine-related organizations and Appendix 9 for a summary of all key accomplishments described by individual researchers.

Development of an acellular pertussis vaccine: From basic research to manufacture

In the late 1990s, sanofi pasteur marketed the first acellular pertussis vaccine in the world. It was researched, developed and is manufactured in Canada. The vaccine contains purified antigenic components of the bacterium *Bordetella pertussis*. In addition to protecting against whooping cough, it has other antigens that afford protection against diphtheria, tetanus, polio and *Haemophilus influenzae* type B.

The acellular vaccine (Pentacel™) replaced whole-cell pertussis vaccines introduced in the 1940s. Although the older vaccines drastically reduced the incidence of pertussis infections, frequent local and systemic reactions, which were occasionally severe, were reported. As well, small outbreaks occurred every three to five years because some individuals were not protected. The acellular vaccine is safer and more effective

than the whole-cell vaccine, has virtually prevented small outbreaks of whooping cough in children over the age of two months and all but eliminated *Haemophilus influenzae* type B infections.

Dr. Scott Halperin at the Canadian Centre for Vaccinology at Dalhousie University and his team participated in the clinical trials associated with the licensure of the vaccine. The vaccine is now licensed in 52 countries around the world, including the United States and the United Kingdom.

Development of vaccine technology against *Neisseria meningitidis* type C

Led by Dr. Harold Jennings, a team of scientists at the NRC developed an innovative technology that attaches a polysaccharide from the bacterium *Neisseria meningitidis* group C to a non-toxic form of tetanus toxoid. *Neisseria meningitidis* group C causes meningitis. A few years ago, approximately 10% of Canadians (many under the age of 5) who contracted meningitis died, while those that survived suffered serious health complications such as deafness or permanent brain damage.

The NRC technology was licensed to Baxter Healthcare Corporation who used it to develop a vaccine called NeisVac-C™. The vaccine replaced previous vaccines that were not very effective in children. NeisVac-C™ was one of three conjugate vaccines that were used in the United Kingdom in the late 1990s to combat meningococcal disease, which at that time was the number one killer of children between the ages of one to five. The vaccines helped to reduce the incidence of disease by about 75%, avoiding an estimated 500 cases and 50 deaths in a two-year period. The vaccine was approved for use in Canada in 2002, where it is manufactured by GlaxoSmithKline Inc.

Preparing for and assessing the impact of HPV immunization in Canada

In July 2006, Merck's quadrivalent recombinant vaccine (Gardasil™), which protects against HPV types 6, 11, 16 and 18, was approved for use in Canada. It is the first HPV vaccine to be licensed for use. HPV types 16 and 18 cause 70% of all cervical cancers and types 6 and 11 cause ano-genital warts.

In 2005, to prepare for the anticipated Canadian approval of vaccines for HPV, PHAC and CAIRE, in partnership with CIHR, held a Canadian HPV Vaccine Research Priorities Workshop, which brought together over 50 Canadian and international HPV experts and researchers from the areas of vaccines, cancer and sexually transmitted diseases to develop national research priorities and identify infrastructure gaps.

One of the areas identified was program delivery research. To address this priority and assess the potential impact of immunization programs, Dr. Babak Pourbohloul at the UBC Centre for Disease Control and Dr. Marc Brisson at Université Laval worked independently to develop mathematical models of HPV transmission and the impact of HPV immunization. The model outcomes helped policy makers make decisions regarding implementation of HPV immunization programs in Canada.

GlaxoSmithKline has developed a bivalent recombinant HPV vaccine to protect against HPV types 16 and 18. It is in the final stages of review at the FDA. Dr. Eduardo Franco at McGill University assisted GlaxoSmithKline during the clinical development phase of the vaccine by co-leading a randomized control clinical trial. His research, which demonstrated the efficacy of the vaccine, was selected by *The Lancet* medical journal as among the most important contributions in medicine in 2006.

Assessment of and new recommendations for influenza immunization programs

Annual epidemics of influenza continue to cause worldwide morbidity, mortality and societal disruption. In October 2000, Ontario initiated the world's first large-scale universal influenza immunization program to provide free influenza vaccinations for the entire population six months of age or older. Dr. Jeff Kwong and his research team at the Institute for Clinical Evaluative Sciences evaluated this program and found decreases in influenza-associated mortality, health-care use (hospitalizations and visits to emergency departments and physician offices), and antibiotic prescriptions relative to other provinces. The results will assist policy makers to develop recommendations for the implementation of influenza immunization programs.

Research results generated by Dr. Noni Macdonald and her team at the Canadian Centre for Vaccinology, Dalhousie University were the basis of a change in policy by NACI who, in 2007, recommended that all pregnant women receive influenza vaccines. The team performed a large study on pregnant women using administrative databases to determine risk of hospitalization and/or physician visit for respiratory illness during the flu season versus risk in the flu season prior to pregnancy. The researchers found that there was a significant increase in risk of serious illness caused by influenza in pregnant women especially in the third trimester.

Development of candidate SARS vaccines

SARS was a new respiratory disease that emerged in China at the end of 2002 and quickly spread to several countries, including Canada. Worldwide, about 8000 people were infected with SARS and 800 people died during the outbreak. An early research

success by Canadian clinicians and scientists was the sequencing of the SARS virus. Building on this knowledge, Dr. Brett Finlay and Dr. Robert Brunham at the UBC Centre for Disease Control co-directed the SARS Accelerated Vaccine Initiative to rapidly develop SARS vaccines. The initiative consisted of a group of over 40 scientists, including researchers at UBC, VIDO and McMaster University. Within six months, the team developed three prototype vaccines using whole killed virus, adenovirus expressing SARS spike protein and recombinant spike protein. Fortunately, human transmission of SARS was halted in July 2003 due to a massive public health effort and further development of the vaccines has not been necessary. The experience, however, allowed the researchers to develop a new way of doing rapid response vaccine development science. If SARS reappears, the vaccines will be developed further.

Development of vaccines against hemorrhagic fevers

In 2005, Dr. Heinz Feldmann and Dr. Steven Jones from the PHAC National Microbiology Laboratory, in collaboration with Dr. Thomas Geisbert from the U.S. Army Medical Research Institute of Infectious Diseases, announced that they had developed vaccines against Ebola and Marburg viruses that had proven 100% effective in protecting monkeys from these often deadly viruses. The viruses are potential public health and bioterrorism threats. The vaccines are based on attenuated recombinant vesicular stomatitis virus vectors expressing either Ebola or Marburg glycoproteins. Pre-clinical trials of these vaccines are underway. Once fully developed, vaccines against these viruses will help stop outbreaks where they originate and reduce the risk of disease spread in the event of a bioterrorism attack.

Development and licensure of a cattle vaccine against *Escherichia coli* O157:H7

The transmission of disease from animals to humans has become a major source of infection in Canada, particularly in high-risk populations. Presently, there are few methods for the control of these diseases. Vaccination of both animal and human populations would have a significant impact on environmental safety (i.e. Walkerton-type outbreaks), foodborne illness and travellers' diarrhea. A major goal of the research conducted by Dr. Andrew Potter and his research team at VIDO is to produce a comprehensive family of vaccines for these types of pathogens that can be used in animals, to lessen the environmental load of these organisms, and in humans, to prevent disease in high-risk populations. To illustrate, the team, in collaboration with Dr. Brett Finlay at UBC, developed a vaccine for *Escherichia coli* O157:H7. The technology has been transferred to the private sector for commercialization. It is anticipated that the *Escherichia coli* O157:H7 vaccine will be in widespread veterinary use in Canada within two years.

Research and development of vaccine adjuvants

Adjuvants are critical components of vaccines: they enhance the immune response to an antigen and have a role in triggering specific types of immune responses. Researchers at GlaxoSmithKline have spent more than 20 years developing adjuvants that will evoke the required type of immune response to a particular antigen. For example, they tested three different adjuvants for their malaria vaccine, which is in clinical trials. They have also developed new adjuvants for pandemic influenza vaccines. A new adjuvant is also being used in their HPV vaccine that is in the final stages of review at the FDA.

In Canada, several individual researchers have also been engaged in developing new

adjuvants. For example, Dr. Denis Leclerc at Université Laval has improved the intrinsic adjuvant properties of papaya mosaic virus-like particles to develop a novel vaccine platform that can trigger both arms of the immune system: cell-mediated and humoral. He and his research team are currently planning to bring the adjuvant into Phase I trials in humans. They believe that, when fully developed, the new system could be used to make a universal influenza vaccine and aid in the development of vaccines that trigger strong cell-mediated immune responses, which will be needed in vaccines for hepatitis C, HIV and cancer.

Dr. Girish B. Patel and colleagues at the NRC have developed an adjuvant and mucosal delivery system using archaeal polar lipids. The system is efficient at eliciting long-lasting mucosal and systemic immune responses upon intranasal vaccination in mice. The technology is being evaluated for applications in human and veterinary vaccines.

Therapeutic cancer vaccines

The first therapeutic vaccine to treat human cancer received Russian approval in April 2008 when the American biotechnology company Antigenics was permitted to market Oncophage for the treatment of kidney cancer. All of the vaccine companies interviewed for this report were developing therapeutic cancer vaccines, and many vaccines are in clinical trials, some at the Phase III stage. In Canada, sanofi pasteur has a cancer vaccine research program that focuses on melanoma and colorectal cancer, and efforts are also being directed at breast cancer. Vaccines that the company has developed employing modified canary pox viral vectors (ALVAC) to deliver tumour antigens or other immunomodulatory molecules are currently in Phase II clinical trials in Canada and elsewhere.

Individual researchers in Canada are also conducting studies to develop therapeutic cancer vaccines. Dr. Jonathan Bramson at McMaster University is developing recombinant adenovirus vaccines that are highly efficient at evoking immunity against cancer antigens in mice. He and his research team are also developing vaccines with dendritic cells (a type of immune cell that stimulates immune responses). The dendritic cells are removed from mice, genetically modified to express tumour cell antigens and then transferred into mice. This approach elicits helper T cell immunity (needed for both cell-mediated and humoral immune responses) and stimulates a unique population of anti-tumour natural killer cells. Given the success of dendritic cell vaccines in pre-clinical models, Dr. Bramson has been working with colleagues at McMaster University (Drs. Yonghong Wan, Ronan Foley, Bindi Dhesy, Graeme Fraser and Mark Levine) to evaluate dendritic cell vaccines in early phase human trials. The group has successfully completed a Phase I/IIa trial for melanoma demonstrating the feasibility of this approach and is in the midst of a similar trial for breast cancer.

Research Strengths

The accomplishments described in this report identify current research strengths in Canada. There is a great deal of strength in early discovery research, especially in the areas of identifying the best antigens to be used in vaccines against infectious agents and for cancer therapy; discovering and developing novel adjuvants and methods for antigen delivery; and in studying the immune system in order to evoke specific types of immune responses and to develop assays to examine immune responses to vaccination. There is also strength in the areas of epidemiology, vaccines for special populations and vaccine evaluation. Approximately 25 infectious agents or diseases were targeted in the

accomplishments described. The most common ones were: influenza, therapeutic cancer vaccines, HPV and HIV. In the case of influenza, HPV and HIV, accomplishments included basic science discoveries, epidemiological findings, development of mathematical models and vaccine evaluation.

Vaccine-Related Challenges and Recommendations

The purpose of this section is to outline vaccine-related challenges in Canada and to provide suggestions on how CIHR-III, its partners and others can address and overcome these challenges. The information is based on the responses made by representatives from vaccine-related organizations, individual researchers and representatives of funding organizations to the following questions:

Representatives from vaccine-related organizations were asked:

- What vaccine-related scientific challenges require attention in Canada?
- How can CIHR-III help to facilitate vaccine-related research in your organization or in general within existing programs?
- How can CIHR-III help in translating your organization's research accomplishments into new products or health services so that they are utilized to their fullest potential?

Individual researchers were asked:

- How can CIHR-III facilitate/support you to be more successful and capitalize on existing opportunities?

Representatives from funding organizations were asked:

- What vaccine-related scientific challenges require attention in Canada?
- How can CIHR-III help in translating vaccine research accomplishments into new

products or health services so that they are utilized to their fullest potential?

The answers have been compiled and categorized. Because many of the recommendations relate directly to the identified challenges, both are presented together. The challenges and recommendations are ordered to follow the chronology of the vaccine research and development continuum (Figure 1), with research planning and basic research

challenges listed before vaccine development and clinical trial challenges. Challenges not directly related to research, and recommendations that do not match a specific challenge are described last. The number of respondents, who made a comment related to the challenge or recommendation, is shown in brackets. (Note that the numbers do not match because challenges and recommendations were described in answers to separate questions.)

Challenge: Research efforts need to be better coordinated (9 respondents)

There are a number of excellent vaccine researchers and specialists in Canada in a number of organizations, but their efforts are fragmented and there is a general lack of communication among different groups. The 2005 decision not to renew funding of the Canadian Network for Vaccines and Immunotherapeutics (CANVAC), a Network of Centres of Excellence that included 75 researchers, contributed to this fragmentation. It eliminated a mechanism for researchers to share ideas and establish collaborations. Related to the need to coordinate research efforts, is a need to identify research priorities for the next five to eight years.

The United States does vaccine research and development well. Basic science research is performed at the National Institutes of Health (NIH), and vaccine trials are then undertaken at associated vaccine trials units and vaccine evaluation centres. Also, the Centers for Disease Control and Prevention (CDC) perform research on the epidemiology of infectious disease and vaccine effectiveness, which supports vaccine research and development.

Recommendation: Organize and facilitate vaccine research workshops and facilitate communication (13 respondents)

CIHR and partners should organize and facilitate workshops to help vaccine researchers and stakeholders identify gaps and set vaccine research priorities, foster cross-disciplinary collaboration and help develop research programs. The workshop for the Safe Food and Water Initiative that was organized by CIHR and partners could serve as a model. That event, which respondents described as a tremendous success, brought together individuals from many areas.

A vaccine research workshop should include basic scientists (microbiologists, immunologists, vaccinologists, etc.), industry representatives, public health experts, clinicians, nurses, members of the National Advisory Committee on Immunization and government representatives. The expanding use of vaccines to prevent and treat diseases such as cancer means that there is a need to include organizations and individuals with expertise in relevant fields in the workshops and discussions.

CIHR and partners should also provide opportunities for knowledge sharing during the research process. Showcasing researchers and their results in this manner would allow stakeholders such as industry and other end users to learn about the research that CIHR and other organizations are funding and help them identify Canadians who can provide scientific guidance in specific areas. Having a database that documents the expertise of Canadian researchers/physicians and their research output would also facilitate the communication of preliminary research results to interested stakeholders.

Recommendation: Foster linkages between all stakeholders (8 respondents)

To coordinate research efforts, CIHR and partners should foster linkages among national and international researchers, public health organizations, industry, end users, decision makers, funding organizations and international research-related organizations. For example, groups such as CIHR, PHAC, HC, industry and others could work together to identify sources of infection and morbidity and determine the best approach to deal with each disease or potential threat. This could take the form of a collaborative consortium modeled on the Canadian HIV Vaccine Initiative, which includes CIHR, PHAC, HC and industry. The CIHR/PHAC collaboration on influenza pandemic preparedness has worked well and could also be used as a model of best practices on how to establish collaborations. One respondent mentioned that he would like to see the Canadian Vaccine Initiative revived and developed further.

There should be continued support for research collaborations between academia and industry including support for clinical trials. Industry should be involved in early-stage discussions regarding vaccine research priorities and needs. One participant suggested that high-level discussions between the Scientific Directors of CIHR-III and CIHR Institute of Population and Public Health and a public sector consortium might foster collaborations with academia and industry.

Recommendation: Establish a vaccine research network (3 respondents)

Respondents suggested that a network of centres of excellence for vaccine research and development should be established. This could be accomplished informally by providing funds for researchers in complementary areas to get together to discuss a project. If the project is large, it will require a project manager/coordinator.

A more formal, integrated, vaccine research centre with a full spectrum of research encompassing basic science, clinical, and population and public health research, as well as Phase I-III clinical trials would be ideal. Current key players, such as the vaccine evaluation centres in Halifax, Quebec City, Montreal and Vancouver, the PHAC National Microbiology Laboratories and VIDO, could be brought together to drive the initiative. The centre would have two mandates: discovery and translation.

Challenge: Vaccine research and development is costly (4 respondents)

It costs \$750 million to \$1 billion to develop a vaccine. Even early-stage research, which is performed by both academic and industry researchers, requires millions of dollars and must be sustained for longer than the typical research grant of three to five years.

The vaccine business is highly competitive: companies are concerned about funding, purchasing, vaccine development and approval times and costs. The multinational nature of the companies means that the needs of individual countries, which are considered a small part of the market, may be ignored. As well, Canadian vaccine prices traditionally have been the lowest in the world because of bulk purchases, so there is less incentive to sell to Canada. On the whole, specific vaccines are developed by companies based on the potential market for the vaccine and projected profits. As a result, Canadian priorities are often no longer considered.

Companies need incentives to do early development work and clinical trials in Canada. Scientific Research and Experimental Development (SR & ED) tax credits help, but they are insufficient. In many cases, a push from others outside of industry is needed. For example, with emerging diseases such as SARS, companies might be reluctant to develop a robust research and development program for a vaccine because of market uncertainty. Similarly, vaccines for the developing world have a greater chance of being developed if there is collaboration in the early stages with government, funding organizations and industry.

Recommendation: Create partnerships with funding organizations, industry, academic institutions and government to drive vaccine research and development

CIHR has funded and facilitated the development of networks, including the Canadian HIV Trials Network, to support research including clinical studies. CIHR and others should continue to establish partnerships with funding organizations, industry, academic institutions and government to drive vaccine research and development in order to meet the needs of Canadians. For example, CIHR could champion vaccine research and development within the context of broader science and technology initiatives or international development activities supported by the Government of Canada. CIHR should also consider partnering with provincial health research agencies to support a coordinated research agenda. Internationally, there has been renewed interest in vaccine research and development. International initiatives have been useful in helping to leverage funds from national sources. For example, it is unlikely that the Canadian HIV Vaccine Initiative would have been established without support from the Bill and Melinda Gates Foundation. Governments should commit funds before international visits and partnerships are established. In addition, information about the existing networks and how they could contribute to the clinical evaluation of promising vaccine strategies developed in Canada would be of tremendous help to many investigators currently developing new vaccines.

All of these partnering activities would provide funds and encourage academic researchers and industry to focus their research activities. This will ultimately lead to the development of new vaccines and technologies for Canada and the rest of the world.

Challenge: There are still several major diseases for which there are currently no vaccines (8 respondents)

The vaccines developed in the last century were generally relatively easy to make. The tough ones remain. Respondents identified the following infectious agents and diseases for which vaccines are needed (the number in brackets indicates the number of times the infectious agent or disease was mentioned): West Nile virus (4), methicillin-resistant *Staphylococcus aureus* (3), HIV (3), hepatitis C (2), cancer (2), avian influenza (2), meningococcal group B (2), respiratory syncytial virus (1), equine encephalitis (1), plague (1), tuberculosis (1), SARS (1), dengue (1) and prions (1). Knowledge about host/pathogen relationships, human immunology and the epidemiology of these and other emerging infectious diseases is needed to develop vaccines.

There is also a need to develop appropriate animal models to test vaccines, and for research on animal reservoirs and vector competencies. Directing research attention to the animal/human interface, and the development of animal vaccines and methods to decrease the populations of vectors such as insects, arthropods and ticks would help to prevent the spread of disease to humans.

Challenge: Improved methods to formulate and deliver vaccines are needed (3 respondents)

Vaccine formulation and delivery are key challenges. For example, research is needed to develop methods to spare antigen, stimulate different types of immunity (e.g. mucosal immunity), vaccinate special populations (e.g. newborns and the elderly) and deliver antigens (e.g. intranasal vaccines, microparticles or skin patches). Newborns are especially important because infants and children receive the majority of routinely administered vaccines. Technologies that are low-cost or make vaccines easier to deliver would be of great benefit in the developing world.

Methods to modulate the immune response to a vaccine, such as the development of new adjuvants, are also needed. Better ways to determine the correlates of protection would be useful for early vaccine development and clinical trials. Surrogate markers of protection are needed when clinical efficacy studies cannot be performed because of the highly pathogenic nature of the infectious agent.

The pain associated with immunization contributes to a negative experience and poor compliance. There is a scarcity of clinical trials on the pain caused from vaccines and modulating impact of different formulations and local anaesthetics. There is also a lack of knowledge on how the physical environment (setting) effects pain felt during immunization and minimal knowledge on pain management in the hours to days post vaccination. Also, national pain management guidelines and educational materials are needed to ensure that vaccines are administered with minimal pain.

Recommendation: Continue to support basic research (6 respondents)

CIHR must continue to support basic research, especially in the areas of microbiology, immunology and vaccinology. Research on pathogens is essential because it identifies critical biological pathways that can be targeted by vaccines. Research on immunology will help to identify ways to modulate the immune system and also provide the basis of technologies to assess correlates of protection. The development of animal models is often suited to academic researchers who examine specific diseases. The research should also include studies on human immune responses to infection. One respondent suggested that vaccine research be included in the recent funding opportunities on immunotherapy with a focus on adjuvants, which are now recognized to be as important as the antigen in vaccines. For example, a systems biology approach could be used to understand how adjuvants successfully modify the immune response during vaccination. Research is also needed to determine the optimal ways to manage pain during immunization and on how to communicate the results to health-care professionals so that the new research knowledge is applied in the clinical setting. One respondent stated that CIHR should focus on basic research and leave most translational research to voluntary health agencies and to provincial research agencies.

Recommendation: Develop and support strategic vaccine research initiatives (4 respondents)

Respondents were pleased that CIHR-III has made vaccines part of its strategic plan because funding for vaccine research has been underrepresented. One respondent suggested that funds should be focused on two to three areas where Canada can be a world leader instead of funding small grants on a broader range of areas. Others thought that CIHR should introduce strategic funding opportunities to which industry could directly apply. Another thought that CIHR could use existing peer review panels, select highly ranked vaccine applications that missed the funding cut off and provide institute support (similar to the HIV/AIDS initiative) or facilitate partner support for these grants. Strategic initiatives from CIHR should focus on the large infrastructure required to support high quality vaccine research and perhaps provide infrastructure support for translational research groups in different provinces to meet for strategic planning. This could help reduce duplication of expensive translational infrastructure being created in different provinces.

Challenge: The public lacks accurate knowledge about the safety and efficacy of vaccines (7 respondents)

Public concern over vaccine safety has increased over the past ten to 15 years. Paradoxically, part of the problem has been the success of vaccines. Many parents today have never witnessed a major threat of infectious disease. This change in attitude and beliefs has happened in one generation. One of the participants stated that “My parents could not wait to line me up for the polio vaccine.” Health-care professionals and public health experts need to do a better job at educating the public and, in some instances, other health-care providers about the safety and efficacy of vaccines. This is critical because, as one respondent stated, “We can have the best vaccines in the world, but they will remain on the shelf if people do not want them.”

Recommendation: Support behavioural, social and ethics research (8 respondents)

CIHR and partners should support research that examines public perceptions concerning vaccines, and identifies the best methods to inform the public. The Canadian Immunization Guide produced by NACI is a highly technical, 300-page book. Research is needed to determine ways in which the information can be translated so that it is understandable and useful to health-care professionals. Funding opportunities should be developed and aimed at the dissemination of research results. As well, research that models the health and economic impact of vaccines, which is independent of vaccine companies, should be supported. Related to this, vaccine researchers require information to counter the accusations of vaccination critics that they are biased towards industry. This entails promoting the relevant scientific messages concerning the benefit and safety of vaccines and helping to dismiss the myths concerning side effects of vaccination. It also involves providing an ethical framework for researchers conducting vaccine studies. CIHR should provide organizations with funds so that the organizations can communicate information themselves.

Challenge: There is a gap between basic research and Phase I/II clinical trials (4 respondents)

Many academic researchers become stalled relatively early in vaccine development because they lack the resources, expertise, funds and, in some cases, the desire to take their discoveries through pre-clinical trials. For example, an individual researcher can take an antigen, put it in a delivery system and elicit a good immune response in mice, but where do they go from there? Road blocks arise because the vaccine must be produced under stringent GMP for human trials and regulatory approval must be sought. This is intimidating.

In terms of facilities, many researchers do not have access to biosafety level 3 (BSL 3) laboratories or GMP facilities. Although BSL 3 facilities exist, researchers must sometimes wait a year to get in. One respondent said that he had been denied access. Vaccines for emerging diseases and infectious agents, such as avian influenza, prions, SARS and West Nile virus, require researcher access to BSL 3 facilities and will likely require a multidisciplinary approach that involves both academic researchers and industry. As well, it is difficult for researchers to get access to non-human primates for studies.

Adding to these challenges, there is currently no funding mechanism for the later stages of vaccine development. The vaccines of the 21st century will be difficult to create and fiercely expensive due to the technical challenges and rigorous pre-licensure regulatory requirements. Currently researchers have to go to the US or elsewhere to ensure that their discoveries are commercialized. The loss of the immune monitoring facility created by CANVAC was also a big setback.

Recommendation: Partner with industry to bridge the gap between basic science and clinical trials (13 respondents)

If academic researchers could progress further through the vaccine research and development continuum and demonstrate the potential of their discoveries, there would be a greater chance that the research knowledge would be taken up by industry for vaccine development. This might be accomplished via strategic initiatives through industry. CIHR should allow industry to fund a strategic initiative, in order to get them more involved and facilitate vaccine development. Industry should be involved at the application phase because they know what is required in the later stages.

NRC does a good job in partnering with industry to get discoveries into the marketplace. NRC may be able to provide expertise to CIHR in this regard. One respondent stated that he would like to see consultation with end users and the private sector early in the research development stages. If industry is on board early and progress can be made more quickly, it is likely they will be motivated to continue the project. Another respondent said that there is expertise and facilities to do pre-clinical work in Canada, but researchers and industry have to work together to have an impact.

CIHR should also consider becoming involved in the pre-clinical stages of vaccine development. Traditionally, CIHR has directed its investment at the basic level, but has stopped long before a discovery gets to Phase I and II clinical trials.

Recommendation: Establish facilities and guidelines to allow researchers to take discoveries towards clinical trials (2 respondents)

A transitional facility should be established to take discoveries from the laboratory to pre-clinical trials. The facility should contain BSL 3 laboratories to test vaccines in animal models and have the equipment for making vaccines according to GMP. This would allow for the final stage of development of candidate vaccines including late-stage clinical trials. This approach would be more likely to attract investments, because the work will have been done according to GMP. The facilities could be part of a vaccine manufacturing research centre, which would attract industry.

Some trials need access to existing GMP vaccine production at BSL level 2. Limited availability exists (e.g. McMaster) for small-scale manufacture of clinical lots of vaccines for Phase I/II trials in Canada. Such facilities could be incorporated into a national approach thus avoiding duplication of existing efforts.

The NIH and FDA in the US have developed clear guidelines and procedures for the initiation of clinical trials and most vaccine Phase I clinical trials are conducted there. The development of clear guidelines as well as a central point to help move forward towards clinical evaluation of candidate vaccines in Canada would also greatly facilitate the emergence of novel vaccines and technologies.

Recommendation: Create new funding mechanisms to bridge the gap between basic science and clinical trials (2 respondents)

If CIHR were to increase funding for translational research, basic investigational research likely would be compromised – which is not acceptable. A separate funding envelope should be opened to support a competitive funding process aimed at translational investigations. In the case of cancer immunotherapies, for example, this could involve partnering with the National Cancer Institute of Canada (NCIC) and other interested parties. For these types of grants, researchers should be asked to provide a knowledge translation plan in the grant application that includes a detailed process for commercialization. This process should be clearly reflected in the budget, with requests for the necessary support. For example, necessary personnel to commercialize research may include: a technical expert with experience in developing products, someone to help with the patenting process and possibly someone with business expertise to manage the process.

Challenge: There are many clinical research questions that require public funding (5 respondents)

Many vaccine-related clinical research questions are of more interest to public health and governments than industry. Examples include:

- Are fewer doses of a vaccine effective?
- Why are there low coverage rates in certain groups?
- Would it be possible to develop delivery methods that combine vaccines?
- Why have there recently been so many cases of mumps among the vaccinated in Nova Scotia?
- Which company has the best vaccine against a specific disease?
- What is the best way to vaccinate special populations such as pregnant women, Aboriginals, people infected with HIV, the very young and the elderly?
- What is the role of persistent exposure to naturally occurring infectious agents in maintaining immunity?
- Are vaccines compatible and can products be interchanged?
- What is the long-term effect of HPV vaccination on cervical cancer rates?

Public funding is needed to support research to answer these and other questions. The answers will help governments and others make informed decisions regarding the purchase of vaccines and delivery of immunization programs.

In addition, there is an assumption of capacity for vaccine evaluation in Canada, but each of the four main evaluation centres is economically fragile and living a day-to-day existence. The capacity could disappear overnight. For example, those developing pandemic influenza vaccines assume that evaluation centres will be available to evaluate the vaccines, but this is

not a given. Program and safety evaluation research conducted independently from vaccine companies is likely to be better accepted by the public. This type of information is also needed by vaccine providers.

Another related difficulty is that clinical trials are discrete. Researchers cannot go onto the next one without ongoing funding. Stopping and starting means that teams have to be dismantled and then rehired.

Recommendation: Provide additional and ongoing support for pre-clinical and post-licensure vaccine trials (9 respondents)

CIHR should consider providing support for research that addresses the clinical questions outlined. As well, PHAC and provinces should join together to support this type of clinical research. In Quebec, for example, 1% of funds for immunization programs are directed towards specific clinical questions related to vaccines and immunization programs. This model works well and should be considered by other provinces. Ultimately, it is the government that buys vaccines and accurate information is needed to inform these decisions.

Since Canada has excellent health-care databases and good screening, agencies should facilitate use of the information for long-term, follow-up studies of vaccine efficacy. Vaccine evaluation centres should be provided with funds for operating expenses to ensure that clinical trial capacity is maintained. Canada should also foster development of clinical trial capacity in developing countries. For example, this would give them the capability of doing high quality clinical HIV vaccine trials.

CIHR (with PHAC) should consider the funding of a small number of “centres” for the in-depth evaluation of vaccine adverse events. Contingency funding should be available to address new allegations of adverse events quickly.

Additional challenges

Respondents identified additional vaccine-related challenges in Canada that are not specifically related to research, and therefore, fall outside the mandate of CIHR-III. These are listed below.

Up-to-date and standardized data on the epidemiology and burden of disease is often lacking (2 respondents)

There is a need to ensure that methods of detecting disease-causing agents are standardized across all public health laboratories and that the results are available to decision makers and industry in a timely manner. For example, the development of vaccines against meningococcus and pertussis require knowledge of the current, most prevalent serotypes, but there is a three-year lag in the reporting of this information. Up-to-date information should be provided via a high quality nation-wide immunization registry. The Manitoba/Quebec registry is excellent and could serve as a model.

It is increasingly difficult for industry to do clinical trials in Canada (3 respondents)

In the past, Canada was a large contributor to vaccine trials, but the number of trials has eroded because of the length of time to get ethics approval, prolonged times to recruit subjects and overhead costs. Instead, companies are turning to countries where trials will be of good quality, low cost, and can be performed quickly. Canada has the quality, but not the latter two criteria. For example, it took one company three to four months to enroll 600 patients for a vaccine trial in Canada. In contrast, 300-400 subjects were enrolled in one day in Poland because parents do not have access to universal vaccine programs and want their children vaccinated. One way to keep vaccine trials in Canada is to coordinate ethics boards for all sites (i.e. have a common protocol). This would allow trials to get started more quickly. It currently takes about eight weeks for ethics approval (in some universities it can take up to six months). Four weeks would be better. Timing is crucial for seasonal influenza. There should be a single place to go to for ethics approval for all academic networks in order to speed the process. We need to attract more clinical studies including global vaccine trials to Canada. To do this, we should emphasize the quality of our clinical research, the multi ethnicity of our inhabitants, our robust medical databases and universal health-care system.

Faster and more transparent vaccine approval is needed by industry (3 respondents)

Industry needs both good quality and timely review by regulators. The recommendations by NACI should be timely and grounded in research knowledge. Part of the problem is that regulatory groups are under-funded. As well, manufacturers need to know why an application was rejected, but usually they are not given any reasons for rejection. Approval is required from several bodies such as the Patented Medicine Prices Review Board, Common Drug Review and HC, and companies wonder whether this effort is worth the small market share. Industry representatives also would like to have better working relationships with public health agencies and decision makers, especially scientists and clinicians, so that industry can better explain the scientific reasons for recommended vaccine doses and schedules.

Canada must retain and develop its own vaccine production facilities (2 respondents)

We should not be at the mercy of other countries for our vaccine supply. The need for self-sufficiency will be critical in a time of crisis when countries will supply their own citizens with vaccines before shipping vaccines to another country. One way to accomplish this would be to create a critical mass of vaccine centres to attract vaccine companies and big pharmaceutical companies.

Immunization programs across the country need to be harmonized (6 respondents)

Several respondents stated that immunization programs across Canada are fragmented; each province and territory funds a different set of vaccines and has its own vaccine schedule and suggested population groups. A more harmonious structure is needed because the current approach is confusing and complicated. It also makes it difficult to immunize individuals who move from one region to another. It would be useful to develop a national funding platform for immunization programs. The National Immunization Strategy needs to be refreshed. NACI requires up-to-date information about the burden of disease. Its members should have special expertise, such as a high-level understanding of immunology, to make informed decisions regarding complex new vaccine technologies (e.g. new adjuvants). Related to this, efforts should be made to ensure equitable access to existing, under-utilized vaccines.

Additional recommendations

Respondents made two additional recommendations that were not directly linked to the vaccine-related challenges that they had identified. These are listed below.

Improve the grant application process, review and approval times (12 respondents)

CIHR should create a faster application and review process for grants so that research can be performed in a timely fashion. Some research questions, especially those of a clinical nature, require immediate answers. One respondent suggested that the grant application itself be streamlined and made more user-friendly. For example, it took her a long time to complete the common CV section. Another felt that there should be more flexibility with the current grant system, because it is difficult to get funds for research that falls under both CIHR and NSERC mandates. For example, researchers working on animal vaccines against *E. coli* O5187 have found it difficult to get money from either agency. One respondent suggested that CIHR set up a review panel with experts that understand all aspects of vaccine research including transitional research projects. He stated that the lack of expertise on current panels has been frustrating. Another asked that the review process be made more transparent and that better efforts be made to communicate priorities. Regarding specific programs, one respondent thought that the proof of principle program was useful for supporting translational research, but the amount of the grants and their duration should be increased to enhance researcher success. Respondents thought that the requirement to have application outlines approved in the CIHR clinical trials program should be removed because it adds at least six months to the grant approval time.

Train more vaccinologists and develop additional scientific and regulatory expertise (3 respondents)

CIHR has a good program to support training and should use it to train individuals in the areas of vaccinology, emerging diseases, wildlife management in relation to vectors of disease, and other areas relevant to vaccines and immunization programs. Many current vaccinologists are more than 50 years of age, so new researchers must be trained, and ways to retain older researchers should be considered. In this regard, partnerships with vaccine companies could be established to create additional endowed chairs and provide salary support for students, post-doctoral fellows and junior investigators. There is also a need to develop scientists with strong regulatory expertise so that they will be able to make informed recommendations to decision makers in the health-care system. Individuals with high-level scientific knowledge and a thorough knowledge of regulatory affairs will also be necessary for vaccine review panels, especially considering the current and projected advances in vaccine technology.

Funding

A number of funding agencies and organizations that support their vaccine-related research were identified by representatives from vaccine-related organizations and individual researchers (see Appendix 4). A representative from each funding agency and organization was contacted and asked to provide information about their organization's vaccine research investments. Table 2 lists the names of the agencies and organizations that responded, their vaccine-related research priorities, the amount they invested in vaccine research in fiscal year

2007-2008 and future funding commitments. Information for this section came from answers to the following questions:

- Provide a list of your organization's current vaccine research grants and awards, including the amount disbursed between April 1, 2007 and March 31, 2008.
- Has your organization committed future funding to vaccine research? If so, please provide annual totals.
- What are your organization's vaccine research priorities?

Table 2: Organizations that support vaccine research and development in Canada, their vaccine-related research priorities, recent investments and future commitments

| Funding agency/ organization | Vaccine-related research priorities | Funding in fiscal year 2007-2008 | Future funding already committed |
|--|---|---|---|
| Federal | | | |
| Canadian Foundation for Innovation (CFI) (funds research infrastructure at institutions, colleges and research hospitals) | Funding discipline-specific research activities is beyond the scope of CFI, but health research is currently a top priority. | \$684,877 (represents 40%: a matched funding partner is required). | None, however, \$440,000,000 is committed over the next two years to the Research Hospital Fund (a part of which will undoubtedly support vaccine research). |
| Canadian Institutes of Health Research (CIHR) | Related strategic priorities: Pandemic influenza preparedness, HIV/AIDS, Vaccines of the 21 st century, Emerging infections and microbial resistance. | \$23,000,000 | 2008-2014: \$48,000,000 |
| Defense Research and Development Canada (DRDC), Department of National Defense | Novel platforms for rapid, post-exposure immunization and broad spectrum vaccines. Advanced development, support for Canadian licensure and acquisition of initial stockpile. | \$4,040,000 | 2008-2010: \$8,500,000 |
| The Global Health Research Initiative (GHRI) a partnership between CIHR, HC, International Development Research Centre (IDRC) and CIDA | No vaccine priorities as such, but rather supports innovative research as it relates to strengthening health systems and building global health research capacity. | \$1,290,678 HIV Prevention Trials Capacity Building Grants Program launched in 2006. | 2008-2012: \$17,000,000 |

Table 2 continued

| Funding Agency/ Organization | Vaccine-related research priorities | Funding in fiscal year 2007-2008 | Future funding already committed |
|--|---|---|---|
| National Research Council of Canada (NRC) | Priorities include: adjuvants, immunomodulation and vaccine delivery; glyco-vaccine strategies for childhood diseases; and vaccine strategies for intracellular pathogens. | \$5,200,000 | \$5,200,000 per year |
| Provincial | | | |
| Alberta Heritage Foundation for Medical Research | Not a named priority area. | \$250,000 | 2008-2012: \$5,000,000 |
| Fonds de la recherche en santé du Québec (FRSQ) | None in particular. | \$2,268,451 | None. |
| Genome British Columbia (BC) | Vaccine research is not a specific priority, but research proposals within the framework of competitions either within Genome Canada, or Genome BC research competitions are welcome. | Not provided. | Not provided. |
| Manitoba Health Research Council | No funding targeted specifically to vaccine research. | \$228,930.00 | Not provided. |
| Medical Research Fund of New Brunswick | None. | None. | None. |
| Nova Scotia Health Research Foundation | None at this time. | \$78,325 | None. |

Table 2 continued

| Funding Agency/ Organization | Vaccine-related research priorities | Funding in fiscal year 2007-2008 | Future funding already committed |
|--|---|--|--|
| Ontario Institute for Cancer Research (OICR) | Support research on vaccines or other immunological attacks of cancer and clinical trials of cancer vaccines. A major strategic research priority is biotherapies. This program, led by Dr. John Bell in Ottawa focuses on oncolytic viruses and on adoptive immunotherapy approaches from the group at McMaster University. Also have a commercialization program to invest (up to \$500,000) in promising new therapies with a goal of either developing an industry partnership or creating a new company in Ontario. | \$1,653,804 (Competitive grants) \$3,000,000 to \$4,000,000 (Biotherapy priority) | Usually fund one or two competitive grants each year. The grants are approximately \$500,000, spread equally over three years. \$3,000,000-\$4,000,000 (Biotherapy priority) |
| Saskatchewan Health Research Foundation | Public health including infectious disease, water safety and food safety is one of the foundations five priority areas. | \$884,720 | Committed future funding to vaccine research. Preference is given to research that falls into a priority area, but there is no annual total that is allotted for each one. |
| International | | | |
| Bill and Melinda Gates Foundation | Acute lower respiratory infections, diarrheal diseases, HIV, malaria, neglected tropical diseases and tuberculosis. | \$4,510,133 (Canada) \$214,969,511 (total) | 2008-2014: \$9,031,422,263 (total) |

Table 2 continued

| Funding Agency/ Organization | Vaccine-related research priorities | Funding in fiscal year 2007-2008 | Future funding already committed |
|---------------------------------|---|---|-------------------------------------|
| Private sector | | | |
| Dow AgroSciences | Animal health vaccines. Strategic alliance with NRC and research collaborations with Plantigen, SemBioSys and Agrisoma. | Confidential | Confidential |
| Merck Frosst Canada Ltd. | Working with Canadian academic and clinical researchers to build the body of evidence supporting the complete vaccine research and development life-cycle. Includes epidemiologic research and outcomes-based research to document the Canadian burden of illness and health-care resource utilisation and clinical research studies on safety and efficacy as well as post licensure surveillance and evaluation of immunization programs. | In Canada, \$2,125,000+ to support research collaborations, clinical trials, in-kind contributions and investigator-initiated research projects spanning several different vaccine-related therapeutic areas. | \$1,250,000+ per year. |
| sanofi pasteur | | | \$3,800,000 |
| Wyeth Canada | In Canada: ongoing surveillance studies on invasive and non-invasive pneumococcal disease, and ongoing participation in a global study with a new pneumococcal conjugate vaccine. Globally: Wyeth Vaccines developing new vaccines for meningococcal B disease, <i>Staphylococcus aureus</i> , HIV, hepatitis C and B-hemolytic <i>Streptococcus</i> . | \$825,000+ (support to academic researchers, including investigator-originated proposals, two vaccine chairs and one fellowship). | \$695,000 to \$895,000 per year. |

Existing Funding Opportunities

Individual researchers were asked to describe the existing opportunities that would allow them to take their research accomplishments to the next stage. Most of the researchers stated that they intend to apply to CIHR for additional funding support. They listed several programs and initiatives within CIHR including proof of principle, knowledge translation, team and catalyst grant programs, as well as targeted initiatives including pandemic preparedness and HIV. Other funding agencies to which researchers intend to apply include: NIH, NCIC, NSERC, the Bill and Melinda Gates Foundation and the Quebec Department of Health and Social Services (MSSS). Other researchers intend to form partnerships with the private sector. A few stated that there were no existing opportunities to take their research accomplishments further because of meagre support for areas such as clinical trials, surveillance or knowledge translation. One respondent stated that the provinces and territories have decided to allocate 2% of federal money for HPV vaccination to research and program evaluation and suggested that CIHR would be an ideal place to administer the requests for applications.

New Funding Opportunities

Representatives from funding organizations and from vaccine-related organizations identified new funding opportunities for vaccine research. These are described below.

Pandemic Influenza Preparedness

Pandemic influenza preparedness is a strategic research priority of both CIHR and PHAC. Together, they are already supporting critical research in this area. CIHR and PHAC recently announced a new funding opportunity to support an Influenza Research Network. The Network will conduct applied public health research with the goals of developing and testing methods to rapidly evaluate candidate pandemic influenza vaccines for safety and population-based methods to evaluate vaccine effectiveness and safety following release of a pandemic vaccine for general use. The deadline for the letter of intent was May 1, 2008. See the CIHR-III website for more details about this funding opportunity (<http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=360&language=EE&fodAgency=CIHR&view=browseArchive&browseArc=true>).

Canadian HIV Vaccine Initiative (CHVI)

Several funding opportunities will be launched under this new initiative. CHVI will focus on five areas:

- Discovery and social research (\$22 million);
- Clinical trials capacity building and networks (\$16 million);
- Pilot scale manufacturing facility for clinical trials (\$89.1 million);
- Policy and regulatory issues, community and social dimensions (\$8.5 million); and
- Planning, coordination and evaluation (\$3.4 million).

A funding opportunity for pilot scale manufacturing of clinical trials was announced in April 2008. The deadline for the letter of

intent was June 10, 2008. See the CHVI website for more details about this initiative (<http://www.chvi-icvv.gc.ca/index-eng.html>).

Canadian International Immunization Initiative Phase 2 (CIII2)

This is a Canadian International Development Agency (CIDA)- funded initiative in partnership with the World Health Organization (WHO), the United Nations Children’s Fund (UNICEF), the Pan American Health Organization and the Canadian Public Health Association. Phase 1 of

CIII was initiated in 1998 to increase and intensify routine immunization for all children of the world. Phase 2 of the initiative supports research to increase access to and enhance immunization services in CIDA’s priority countries. The CIII2 program is being expanded to include Haiti (\$1 million over five years), and there are preliminary negotiations to launch a subsequent phase of funding for CIII2, but details concerning its focus have not been announced.

Recent vaccine-related developments

Several announcements regarding vaccine research, development and manufacture were made in early 2008 after the survey phase of this report was completed.

The Pan-Provincial Vaccine Enterprise (PREVENT)

In February 2008, PREVENT, one of 11 new Centres of Excellence for Commercialization and Research was announced. It will be an incorporated, non-profit organization that will conduct pre-clinical and proof-of-concept clinical trials for promising early-stage vaccine candidates. Beginning operation in mid-2008, PREVENT will capitalize on expertise at VIDO at the University of Saskatchewan, the Canadian Center for Vaccinology in Halifax and the UBC Centre for Disease Control. By partnering with Canadian stakeholders and shouldering the risk of early-stage vaccine development, PREVENT will strengthen Canada's vaccine industry, promoting growth, investment and improved global competitiveness.

Sanofi Pasteur Human Vaccine Challenge Unit at the Canadian Center for Vaccinology

Also in February 2008, the IWK Health Centre Foundation announced a \$3.8 million donation from sanofi pasteur to the Canadian Center for Vaccinology. \$1 million of the donation will support the completion of the construction of the Sanofi Pasteur Human Vaccine Challenge Unit at the Canadian Center for Vaccinology. The purpose of this facility is to do very early clinical trials on candidate vaccines. The Sanofi Pasteur Human Vaccine Challenge Unit will be a 5,400 square foot, ten-bed, in-

patient facility with isolation rooms, including full disease containment and full physiological monitoring. The remaining \$2.8 million of the donation will support the Canadian Maternal Immunization Study, which will determine whether immunization of pregnant women against pertussis will protect newborns from developing whooping cough.

Canadian Network on HPV Prevention

The Canadian Network on HPV Prevention, hosted by the International Centre for Infectious Diseases (ICID), is in development. Some of the proposed activities of the network include: funding identified HPV research priorities, building capacity within the HPV community, facilitating the evaluation of implementation strategies and enabling knowledge translation to clinical practice and to the public. The overall goal of the network is to improve the health of Canadians by optimizing prevention strategies and technologies related to HPV-associated diseases.

New Research Facilities at sanofi pasteur in Toronto

In April 2008, sanofi pasteur announced that it is investing \$100 million in a new, state-of-the-art research facility at their Connaught Campus in north Toronto to boost innovation in vaccine research for the benefit of global health. The investment includes the construction of an \$80 million facility, the purchase of specialized research and development equipment, and support for research and development jobs over the next five years.

Interdisciplinary Team Grant in Vaccine Design and Implementation

Also in April 2008, the Alberta Heritage Foundation for Medical Research (AHFMR) announced that it had awarded an AHFMR Interdisciplinary Team Grant in Vaccine Design and Implementation to researchers at the University of Calgary, the University of Alberta, the University of Saskatchewan and the University of Toronto. The initiative, led by Drs. Anthony Schryvers, Lorne Babiuk and

James Kellner, will study how the bacteria evolve within the human population in order to design vaccine products capable of providing protection against different strains and species. They will use a detailed understanding of basic biology to target essential processes shared by different disease-causing bacteria. At the same time they will improve vaccine evaluation strategies and develop new approaches to predict the impact of vaccines.

Conclusion

Canada continues to make significant contributions to vaccine research and development. These accomplishments have saved lives, decreased human suffering, reduced health-care costs and protected the health of societies both in Canada and around the world. Several vaccine-related challenges remain, but exciting new funding initiatives and a renewed interest in vaccines make this an ideal time for CIHR-III to launch its Vaccines of the 21st Century Strategic

Research Initiative. It is essential that Canada maintain this new-found enthusiasm by continuing to support and develop both basic and clinical vaccine research, promote vaccine development, and ensure that the country retains its own vaccine manufacturing capability. Many individuals, organizations and countries will have to work together to make the vaccines of the 21st century a reality.



Next Steps

This report will be distributed widely to all those with an interest in vaccine research and development and in immunization. CIHR-III will use the report to develop an action plan and partnerships for the Vaccines of the 21st Century Strategic Research Initiative. The goals of the Initiative are to help coordinate research efforts, foster

linkages, facilitate vaccine research and development and support the transfer of research knowledge to governments, health-care providers and the public. These activities will take vaccine research and development in Canada to the next level, and ultimately, improve the health and well-being of individuals in Canada and the rest of the world.



Appendices





Appendix 1: *Representatives Interviewed from Vaccine-related Organizations*

| Name | Position | Affiliation |
|-------------------|---|--|
| Mary Appleton | Senior Manager | Canadian Coalition for Immunization Awareness and Promotion |
| Lorne Babiuk | Vice President (Research) | University of Alberta |
| Luis Barreto | Vice President, Public, Scientific and Medical Affairs | sanofi pasteur |
| Mary Ewasyshyn | Senior Director, R&D Strategic Initiatives | |
| Gordean Bjornson | Member, Management Committee | Canadian Association of Immunization Research and Evaluation (CAIRE) |
| Judith BossÈ | Vice-President, Science Branch | Canadian Food Inspection Agency |
| Robert Brunham | Director | University of British Columbia Centre for Disease Control |
| Marie AdÈle Davis | Executive Director | Canadian Pediatric Society |
| Joy DasGupta | Senior Scientific Advisor, Influenza | GlaxoSmithKline Inc. |
| Scott Simpson | Scientific Advisor, Pediatric Vaccines | |
| Bruce Seet | Scientific Advisor, HPV/HSV Vaccines | |
| David Evans | Chair, Department of Medical Microbiology and Immunology | University of Alberta |
| Ross Findlater | Member, CIC and Saskatchewan Chief Medical Health Officer | Canadian Immunization Committee (CIC) |
| Richard Garant | Executive Director, Vaccine Group | Merck Frosst Canada Ltd. |
| Graeme Fraser | Manager, Policy and Research | BIOTECanada |

Appendix 1 continued

| Name | Position | Affiliation |
|------------------|--|---|
| Scott Halperin | Director | Canadian Centre for Vaccinology/Clinical Trials Research Center, Dalhousie University |
| Kent Harding | Chief Scientist | Defence Research and Development Canada |
| Arlene King | Director General, Centre for Immunization and Respiratory Infectious Diseases | Public Health Agency of Canada |
| Monique Landry | Member, CIC and Medical Officer of Health, Quebec | Canadian Immunization Committee (CIC) |
| Frank Plummer | Scientific Director General, National Microbiology Laboratory | Public Health Agency of Canada |
| Andrew Potter | Director | Vaccine and Infectious Disease Organization |
| Jim Richards | Director General | National Research Council of Canada Institute for Biological Sciences |
| Martin Schechter | National Director | Canadian HIV Trials Network |
| David Scheifele | Chair | Canadian Association of Immunization Research and Evaluation (CAIRE) |
| Steven Sternthal | Head, Canadian HIV Vaccine Initiative Secretariat, Acting Director, Office of HIV Vaccines | Canadian HIV Vaccine Initiative Secretariat |
| Rob Van Exan | Vice-chair, VIC and Director of Immunization Policy, sanofi pasteur | Vaccine Industry Committee (VIC) |
| David Wortzman | Director of Medical Affairs | Wyeth Canada |

Appendix 2: Interview Questions for Representatives from Vaccine-Related Organizations

- 1) Please briefly describe the vaccine-related research programs of your organization.
- 2) What funding agencies support research in this area at your organization?
- 3) What are the major accomplishments that your organization has made in the area of vaccines and immunization programs over the past five years? Please provide the name of a lead person to contact to get additional information on each accomplishment.
- 4) What are the anticipated or realized impacts of the research accomplishments of your organization?
- 5) How can CIHR-III help to facilitate vaccine-related research in your organization or in general within existing programs?
- 6) How can CIHR-III help in translating your organization's research accomplishments into new products or health services so that they are utilized to its fullest potential?
- 7) What vaccine-related scientific challenges require attention in Canada?
- 8) Is your organization involved in the international vaccine arena and do you have partnerships or collaborations with international organizations?

Appendix 3: Web Survey Questions for Individual Researchers

Name:

Position:

Institution:

Summary of key research projects and accomplishments.

(Please select your top one to three research projects/accomplishments from the past five years.)

Title of research project:

Example: SELDI-ToF MS in blood-borne protozoan infections: novel diagnostic approach and new insights into host-parasite interactions. (We thank Dr. Brian J Ward, Research Institute of the McGill University Health Centre for providing the example.)

Identified need for project:

Example: Despite major changes in the practices and screening procedures for Canada's blood supply system, the system remains vulnerable to a number of infections, in particular, protozoan parasites such as Chagas disease and malaria. These parasites can live in humans for many years without sign of illness and, at present, there are no blood screening assays for these parasites.

Goal of project:

Example: The research team planned to use a relatively new form of mass spectrometry to scan sera from subjects with different parasitic diseases. The goal was to identify individual parasite-origin proteins or protein patterns which would help positively diagnose the presence of parasites.

Accomplishments/Outcomes:

Example: The researchers were able to use this technique to identify protein patterns or individual proteins that had been altered in each of the major parasitic diseases. They also succeeded in engineering antibodies against several of the unusually-shortened human proteins.

Anticipated or realized impact of research project:

Example: This brings the team a step closer to developing a screening test that could be adapted for use with existing high-throughput screening platforms used by blood banks.

If results of this project have been published, please provide the full citation:

Please use the following format: Rioux MC, Carmona C, Acosta D, Ward B, Ndao M, Gibbs BF, Bennett HP and Spithill TW. 2008. Discovery and validation of serum biomarkers expressed over the first twelve weeks of *Fasciola hepatica* infection in sheep. *Int J Parasitol.* 38:123-136.

Funding organizations that supported this research:

(Please include approximate percentage contributed by each organization)

What existing opportunities are there to support taking this research accomplishment to the next stage?

How can CIHR-III facilitate/support you to be more successful and capitalize on existing opportunities?

Appendix 4: *Funding Agencies and Organizations Who Were Contacted*

| Funding agency/organization |
|--|
| Federal |
| Beef Industry Development Fund (BIDF) |
| Canadian Breast Cancer Research Alliance |
| Canadian Cancer Society |
| Canadian Foundation for AIDS Research (CanFAR) |
| Canada Foundation for Innovation (CFI) |
| Canadian HIV Trials Network (CTN) |
| Canadian Institutes of Health Research (CIHR) |
| Canadian International Development Agency (CIDA) |
| Cancer Research Society |
| Chemical, Biological, Radiological, and Nuclear Research and Technology Initiative |
| Defense Research and Development Canada (DRDC), Department of National Defense |
| Health Canada (HC) |
| The Global Health Research Initiative (GHRI) a partnership between CIHR, HC, IDRC and CIDA |
| Krembil Foundation |
| PrioNet Canada |
| Public Health Agency of Canada (PHAC) |
| National Cancer Institute of Canada |
| National Research Council of Canada (NRC) |
| Natural Sciences and Engineering Research Council (NSERC) |
| The Advancing Canadian Agriculture and Agri-Food Program |

Appendix 4 continued

| Provincial |
|--|
| Agriculture Development Fund, Saskatchewan |
| Alberta Heritage Foundation for Medical Research |
| Alberta Livestock Industry Development Fund (ALIDF) |
| Department of Agriculture, Alberta |
| Department of Agriculture, Saskatchewan |
| Department of Health, Nova Scotia |
| Fonds de la recherche en santé du Québec (FRSQ) |
| Genome BC |
| Government of Saskatchewan Advanced Education and Employment |
| Institut national de santé publique Québec |
| Manitoba Health Research Council |
| Medical Research Fund of New Brunswick |
| Michael Smith Foundation for Health Research |
| Ministère de la Santé et des Services sociaux |
| Newfoundland and Labrador Centre for Applied Health Research |
| Nova Scotia Health Research Foundation |
| Ontario HIV Treatment Network (OHTN) |
| Ontario Institute for Cancer Research |
| Prince Edward Island Health Research Authority |
| Saskatchewan Health Research Foundation |

Appendix 4 continued

| |
|---|
| International |
| Bill and Melinda Gates Foundation |
| Human Frontiers in Science Program |
| National Institute of Allergy and Infectious Diseases (NIAID) |
| National Institutes of Health (NIH) |
| Private sector |
| DowAgro Sciences |
| GlaxoSmithKline Inc. |
| Immune Response Corporation |
| Merck Frosst Canada Ltd |
| sanofi pasteur |
| Wyeth Canada |

Appendix 5: Questionnaire for Representatives of Funding Organizations

Please use as much space as necessary to answer the following questions

1. Name, location and website of organization.
2. Contact name for organization's vaccine research funding.
3. Type of organization (research funding agency, industry, development agency, etc.).
4. Please provide a list of your organization's current vaccine research grants and awards, including:
 - Name of the primary investigator
 - Grant title
 - Amount disbursed between April 1, 2007 and March 31, 2008.

A separate spreadsheet can be attached.

5. Has your organization committed future funding to vaccine research? If so, please provide annual totals.
6. What are your organization's vaccine research priorities?
7. Has your organization established any strategic partnerships with other organizations in the area of vaccine research? (e.g. co-funding or co-designing a research initiative or in designing an initiative to be complementary to one in another organization.) If so, what was the name of the organization that you partnered with, and what was the name of the initiative?
8. How can CIHR-III help in translating vaccine research accomplishments into new products or health services so that they are utilized to its fullest potential?
9. What vaccine-related scientific challenges require attention in Canada?

CIHR-III is grateful for your input in responding to this request. We look forward to sharing the aggregate results with you.

Appendix 6: *Members of the IAB Subcommittee on Vaccines of the 21st Century*

| Name | Position | Affiliation |
|----------------|--|--|
| Luis Barreto | Vice President, Public, Scientific and Medical Affairs | sanofi pasteur |
| James Lavery | Assistant Professor | Department of Public Health Sciences and Joint Centre for Bioethics, University of Toronto |
| Mark Loeb | Professor | Department of Pathology and Molecular Medicine, McMaster University |
| Warren Hill | Senior Research Analyst | BC Centre for Disease Control, Vancouver |
| Allison McGeer | Microbiologist and Infectious Disease Consultant | Department of Microbiology, Mount Sinai Hospital, Toronto |

Appendix 7: Major Vaccine-Related Organizations in Canada: Current Projects and International Linkages

Information for this appendix came from representatives from vaccine-related organizations who were asked the following questions:

- Please briefly describe the vaccine-related research programs of your organization.
- Is your organization involved in the international vaccine arena and do you have partnerships or collaborations with international organizations?

BIOTECanada

Current focus: Working with the Institute for Safe Medical Practices regarding adding bar codes to vials. Have performed an open consultation with stakeholders.

International linkages: Participate with sister organizations such as BIO in the United States and Europabio in Europe. Have been asked to be an observer for review meetings of the Centers for Disease Control Advisory Committee on Immunization Practices.

Canadian Association of Immunization Research and Evaluation (CAIRE)

Current focus: Identifying researchers that could help with vaccine trials and providing a forum to meet with vaccine companies. Would like to provide a culture to make it easier to plan and carry out industry sponsored trials in Canada.

Canadian Center for Vaccinology, Dalhousie University

Current focus: Respiratory pathogens and infections such as *Bordetella pertussis*, influenza, respiratory syncytial virus. Perform clinical trials for vaccines for all sorts of diseases. Focus has also been on children, but also recently on infections in pregnancy and during pregnancy. Also, health policy research concerning vaccinating pregnant women against influenza.

International linkages: Have several linkages. For example: the health policy group is working with Cuban government to determine how they get high rates of vaccine uptake; performing studies to establish a generic protocol for pertussis vaccines with WHO; and examining the effectiveness of a meningococcal program in Africa (non-medical studies).

Canadian Food Inspection Agency

Current focus: Prevention of disease transmission from the animal (wildlife/domestic animal) to human interface. Focus is on vaccinating animals to prevent human disease (e.g. vaccinating animals for rabies). Also evaluate animal vaccines for animal diseases in terms of cost and effectiveness.

International linkages: Work with foreign governments at all regulatory levels. Focus on zoonotics, catastrophic animal diseases, diseases that are exotic to Canada and diseases with bioterrorism potential.

Canadian HIV Initiative

Current focus: Announced a funding opportunity to establish a pilot scale manufacturing facility in Canada to increase the global capacity to produce HIV vaccine candidates for use in clinical trials.

International linkages: Part of the global HIV vaccine enterprise. Work with the International HIV Vaccine Initiative, NIH, WHO, UN South Korean International Vaccine Initiative and newly formed Swiss HIV Vaccine Initiative.

Canadian HIV Trials Network

Current focus: Helping to establish more clinical trial centres in Africa in partnership with CIDA, IDRC and CIHR.

International linkages: In addition to the work described above, interact with international HIV/AIDS organizations. Many collaborations formed from bilateral relationships between individual researchers in different countries.

Canadian Pediatric Society (CPS)

Current focus: CPS runs the Canadian Pediatric Surveillance Program, which asks all pediatricians in Canada to monitor ten selected conditions for a period of two years. Current conditions under study of relevance to vaccine research and immunization programs are: acute flaccid paralysis for polio; congenital cytomegalovirus infection in pregnant women and severe combined immunodeficiency and BCG vaccination in First Nations and Inuit communities. CPS is considering adding community acquired methicillin-resistant *Staphylococcus aureus* and infective endocarditis to the list of conditions to be monitored.

Centre for Immunization and Respiratory Infectious Diseases, PHAC

Current focus: Helped to identify and is supporting pandemic influenza preparedness strategic research priorities. A major funding opportunity will support an Influenza Research Network, which will carry out a specific work plan to develop, test and evaluate the safety and immunogenicity of influenza vaccines and immunization programs. The expected start date for the Network is April 2009. Have also supported the BC Sentinel Surveillance Program, which is studying the effectiveness of influenza vaccines.

International linkages: Work with the WHO. Have bilateral collaborations with the United States and the United Kingdom.

Defence Research and Development Canada

Current focus: Developing vaccines against biological agents that could be utilized in a bioterrorism scenario or against endemic disease threats that could be encountered by the Canadian Forces during deployment abroad. Have developed a rapid-acting vaccine to a member of the alphaviruses, western equine encephalitis, using adenoviral vectors. Component vaccines to brucellosis, glanders

and mellioidosis are being researched. Broad spectrum protection using immune modulators is under development.

International linkages: Co-operate with defence departments of the United States, United Kingdom and Australia in the final development and acquisition of vaccines that are to be used for security reasons including helping to get final regulatory approval.

GlaxoSmithKline Inc.

Current focus: In Canada, doing clinical research on new vaccine products and epidemiological research on the burden of disease to health and economics (e.g. vaccine trials for HPV vaccine, diphtheria/pertussis and rotavirus). Internationally developing cancer vaccines for melanoma and non-small cell lung carcinoma and vaccines for infectious diseases such as malaria and HPV.

International linkages: Company is global. Have links to WHO, Global Alliance for Vaccines and Immunization, Pan American Health Organization. Have partnerships with the Bill and Melinda Gates Foundation and UNICEF.

McMaster Centre for Gene Therapeutics

Current focus : Research on the development of vaccines for therapeutic intervention in cancer using cell-based genetic vaccines. Maximizing potential for dendritic cell-based vaccines and immunomodulation for optimization of the host immune response to tumour antigens. Equal attention being paid to development of vaccine approaches that induce potent protective immunity at the mucosal surfaces of the lung, gut and genitourinary tract for infectious diseases such as TB, HIV and influenza.

International Linkages : Many collaborations in the United States for cancer vaccines and the developing world, including Kenya, with Frank Plummer for HIV studies.

Merck Frosst Canada Ltd

Current focus: In Canada, epidemiological studies for rotavirus, HPV, zoster (burden of disease). Currently have a vaccine trial for zoster with a new format vaccine. Performing research on existing hepatitis vaccines to determine which works better.

International linkages: Many linkages, for example, work with WHO and the Bill and Melinda Gates Foundation to supply vaccines to the developing world.

NRC Institute for Biological Sciences

Current focus: Research on adjuvants (e.g. archaeal lipids), immunomodulation and vaccine delivery; glyco-vaccine strategies for childhood diseases, especially those caused by meningococcal infections; and vaccine strategies for intracellular pathogens (e.g. *Francisella tularensis*).

International linkages: Several international linkages. For example, collaborating with researchers at Oxford University on a meningococcal group B vaccine. Collaborated with sanofi pasteur in France

on an otis media vaccine. Working with Nicholas Piramal India Limited on archaeosome adjuvants. Have collaborations between researchers in Sweden and United States on *Francisella tularensis*. Working with researchers in Czechoslovakia on a vaccine for tick disease.

National Microbiology Laboratory, PHAC

Current focus: Vaccine research into: viral hemorrhagic fevers, influenza, HIV and hepatitis C. Determining what is special about the immune system of people who are highly exposed to HIV, but do not get the disease.

International linkages: Many collaborations. For example, for viral hemorrhagic fevers, working with researchers in the American biodefence field. HIV work is being done in Kenya.

sanofi pasteur

Current focus: Research on novel vaccines for seasonal and pandemic influenza including novel delivery systems, doses and adjuvants. Also engaged in epidemiological surveillance protocols: inter-pandemic and universal vaccine evaluation. Support the work of PHAC and CIHR—with industrial partnerships and northern southern hemisphere exchange. Have a cancer vaccine program working on therapeutic melanoma vaccines. Performing research to modify Menactra vaccine (against pneumococcal disease) so that it can be used in babies less than nine months of age. Developing a vaccine for *Streptococcus pneumoniae* using a protein-based approach to multiple serotypes: this will be a multivalent vaccine against pneumonia. Developing travel vaccines for diseases endemic in parts of the world (e.g. Denge fever, Japanese encephalitis, malaria, West Nile virus). Have an HIV vaccine in clinical trials (Phase I-III), expect results in 2009.

International linkages: Many collaborations. Global company with 100,000 employees.

UBC Centre for Disease Control

Current focus: Epidemiology of vaccine preventable diseases, influenza, *Chlamydia* epidemiology, *Chlamydia* antigen discovery, dendritic cell immunobiology and vaccine design and mathematical modeling of vaccine-preventable diseases.

International linkages: Studying the burden of HPV infection in Uganda. Studying sexual transmission of *Chlamydia* in Africa.

Vaccine Evaluation Centre, BC Children's Hospital

Current focus: Will be starting a major evaluation study in the fall of 2008 examining the effects of using two doses of HPV vaccine instead of three doses. This is a tri-provincial study involving BC, Quebec and Nova Scotia and is funded by these provincial governments. One of the issues will be to develop immunological assays for the evaluation of the vaccine—no serological assays are available outside companies—so this has to be set up. Studying how abnormalities of the innate immune system (e.g. defects in Toll-like receptors) contribute to childhood illnesses such as

infectious and inflammatory diseases. Examining the innate immune system of neonates. Over the past five years have been monitoring for serious adverse effects following influenza vaccination. *International linkages*: Have a new collaboration in Capetown, South Africa working on a prospective cohort study examining genetics and the biology of infectious disease in children, specifically the determinants of infection.

VIDO

Current focus: Zoonotic diseases, emerging infectious diseases and an *E. coli* O1587 animal vaccine with human benefits. Others include: influenza, *Salmonella*, prions, *Campylobacter jejuni*, *Salmonella enterica*, hepatitis C, bovine mastitis and *Mycoplasma bovis*. Developing platform technologies [e.g. immune modulators, DNA vaccines, neonatal immunization (pertussis vaccine) and adenoviral vectors].

International linkages: Have collaborations in 35 countries. For example, with Bill and Melinda Gates Foundation funding have collaborators in United States, India and France. Have three collaborations with research institutes in Russia. Have a collaboration in Germany for influenza research.

Wyeth Canada

Current focus: In Canada, ongoing surveillance studies of invasive and non-invasive pneumococcal disease, and ongoing participation in a global study with a new pneumococcal conjugate vaccine. Globally, Wyeth Vaccines is developing new vaccines for meningococcal B, *Staphylococcus aureus*, HIV, hepatitis C and B-hemolytic *Streptococcus*.

International linkages: Have many collaborations. For example, with GAVI and the Bill and Melinda Gates Foundation want to introduce Prevnar vaccine to Africa, because pneumococcal disease kills one million children in Africa every year.

Appendix 8: Key Accomplishments of Vaccine-Related Organizations

BIOTECCanada

- BIOTECCanada lobbied the federal government to get funding for immunization programs in general. In 2007, the federal government made \$300 million available for HPV immunization programs.

Canadian Association for Immunization Research and Evaluation (CAIRE)

- Many members involved in Immunization Monitoring Program, Active (IMPACT) surveillance program. Demonstrated that following the introduction of *Haemophilus influenzae* type B vaccine in Canada, the number of cases dropped from 500/year to virtually none.

Canadian Center for Vaccinology, Dalhousie University

- Assisted sanofi pasteur in pertussis vaccine development by performing clinical trials on its acellular pertussis vaccine (see “Selected Key Accomplishments”).
- Research results showing that pregnancy increases the severity of influenza infections prompted NACI to recommend in 2007 that pregnant women should receive influenza vaccinations (see “Selected Key Accomplishments” and Appendix 9: Noni Macdonald).
- Vaccine development for respiratory syncytial virus (see Appendix 9: Robert Anderson).

Canadian Coalition for Immunization Awareness and Promotion

- Produced health promotion material related to immunization including a website, pamphlets, posters and information sheets for public health and health-care workers.
- Advocated to government for universal access to vaccines across Canada. In 2007, the federal government made \$300 million available for HPV immunization programs.

Canadian Food Inspection Agency

- Over the past 20 years, promoted rabies vaccines for pets. This has drastically reduced the incidence of rabies in humans.
- The agency vaccinated raccoons against rabies in areas surrounding cities and in highly populated areas. This has prevented the transmission of rabies from raccoons to humans.

Canadian HIV Trials Network

- Have organized a clinical trials network in Canada to rapidly implement vaccines and treatments for HIV. Set a high standard for clinical trials regarding both data on safety and community input in decision making.
- Provided expertise to CAPTN, which is establishing clinical trial capacity for preventative vaccines in Africa. Currently there are seven centres and more are being developed.

Canadian HIV Vaccine Initiative

- Initiative is in the early stages. Main accomplishment to date is getting the initiative up and running.

Canadian Immunization Committee

- Implemented cost-effective vaccine programs that have been approved by NACI.

Canadian Pediatric Society

- Helped establish the National Immunization Strategy.
- Informed pediatricians and public by debunking vaccine myths.
- Advocated for provincially funded immunization programs.
- Produced the publication *Your Child's Best Shot, 2nd edition*, which provides detailed information for parents about vaccines.

Centre for Immunization and Respiratory Infectious Diseases, PHAC

- Identified the need for and helped to develop the National Immunization Strategy.
- Successfully lobbied the federal government for funding for four new immunization programs in 2004 (\$300 million) and for second round of immunization program funding (\$300 million) in 2007, which the federal government decided to direct to HPV immunization programs.
- Organized a workshop to identify research priorities in pandemic influenza preparedness in Ottawa in 2005. The workshop report formed the basis of a multi-year research agenda.
- Organized an HPV vaccine research priorities workshop in Quebec City in 2005 (see "Selected Key Accomplishments").

Defence Research and Development Canada

- Developed a *Brucella* subunit vaccine that has been tested in mice. Require access to BSL3 facilities to do additional testing.
- Have discovered an antigenic component that provides protection against strains of *Burkholderia pseudomallei* (melioidosis).
- A potent immune modulator was found that may have potential as a vaccine adjuvant.

GlaxoSmithKline Inc.

- Have spent more than 20 years working on developing adjuvants that will evoke the required type of immune response against a particular agent or for cancer treatment (see "Selected Key Accomplishments").
- In Canada and globally, GSK is involved with the research and development of influenza vaccines to prepare for a pandemic.

-
- Globally, company is developing several new vaccines including ones for malaria (currently in Phase III clinical trials), TB and HIV.
 - Globally, have 30 vaccines registered.

McMaster Centre for Gene Therapeutics

- First human clinical trial of dendritic cell-based vaccine using cells containing the rodent Her2 gene for the treatment of breast cancer (see “Selected Key Accomplishments”).
- First human clinical trial of dendritic cell-based vaccine using cells containing tumour cell RNA for the treatment of chronic lymphocytic leukemia (see “Selected Key Accomplishments”).
- Developed adenovirus vector-based vaccine for SARS infection targeting both S and N protein in collaboration with SAVI (see “Selected Key Accomplishments”).
- Developed an adenovirus vector-based vaccine for TB that will enter clinical trials in 2009.

Merck Frosst Canada Ltd.

- Globally, researched, developed and recently started to market Gardasil® (vaccine against HPV types 16, 18, 6 and 11) to protect women from developing cervical cancer (see “Selected Key Accomplishments”). Also introduced a rotavirus vaccine and a zoster vaccine.
- In Canada, have performed clinical vaccine trials and epidemiological studies, some in collaboration with academic researchers and health-care professionals, providing data for vaccine development and to aid in future vaccine trials (e.g. rotavirus, HPV, zoster). See Appendix 9: Martin Sénécal, Erich Kliewer, Alain Desmers and James A. Mansi.

National Microbiology Laboratory, PHAC

- Developed three candidate vaccines for viral hemorrhagic fevers that are in pre-clinical trials (see “Selected Key Accomplishments”).
- Early-stage development of a SARS vaccine using a pox viral vector.
- Candidate vaccines for influenza (see Appendix 9: Gary Kobinger).
- Developed viral vectors (adenovirus) for delivering vaccines (see Appendix 9: Gary Kobinger).
- Identified novel antigens for HIV vaccines (Frank Plummer).

NRC Institute for Biological Sciences

- Researched and developed a polysaccharide vaccine for meningococcal group C. It is now being used in the developed world (see “Selected Key Accomplishments”).
- Devised a lipopolysaccharide-based conjugate vaccine platform technology that is currently being used to develop a second generation vaccine against all meningococcal groups, including group B (see Appendix 9: Jim Richards).

-
- Developed and patented novel lipid adjuvants called archaeosomes (see “Selected Key Accomplishments”).

sanofi pasteur:

- In Canada, researched, developed and manufactured an acellular pertussis vaccine. This was the first acellular pertussis vaccine in the world. Canada got access to the vaccine early because the studies were done here (see “Selected Key Accomplishments”).
- In Canada, engaged in Phase II clinical trials for therapeutic cancer vaccines for melanoma and colorectal cancer. ALVAC (modified canary pox viruses) is used to deliver tumour-associated antigens or other immune-stimulant molecules. See “Selected Key Accomplishments.”
- Early stage development of a SARS vaccine.
- Globally, developed Menactra, a meningococcal polysaccharide-protein conjugate vaccine, against *N. meningitidis* serogroups A, C, Y and W-135, to be used in persons 2 to 55. The vaccine was licensed in 2005. This vaccine is used to prevent meningitis in adolescents who are at increased risk of acquiring this infectious disease.
- Make 50% of annual influenza vaccines. Also engaged in epidemiological surveillance of annual influenza to evaluate universal influenza vaccination programs.
- Globally, developed a monovalent polio vaccine that has been successfully used in Egypt and India.
- Globally, developed an injectable polio vaccine.

UBC Centre for Disease Control

- Developed candidate SARS vaccines (see “Selected Key Accomplishments” and Appendix 9: Brett Finlay and Robert Brunham).
- Mathematical modeling of HPV vaccine uptake on cervical cancer rates. See “Selected Key Accomplishments” and Appendix 9: Babak Pourbohloul.
- Identified *Chlamydia* antigens to be used for a vaccine (see Appendix 9: Robert Brunham).

Vaccine and Infectious Disease Organization

- Developed and licensed an *E. coli* O5187 vaccine for cows (see “Key Accomplishments” and Appendix 9: Brett Findlay and Andrew Potter).
- Developed and licensed an animal model of human pertussis infection with newborn piglets. This model is ideal for studying pertussis because it mimics the pathogenesis seen in humans. Now will be able to do significant vaccine efficacy and safety studies, as well as examine neonatal immunization. This is a significant breakthrough because people have tried for decades to get a good model of the human disease. See Appendix 9: Volker Gerdts.
- Demonstrated in animal models that maternal immunization against pertussis is an

effective way to protect the very young against pertussis. Currently recruiting volunteers (pregnant mothers) for a clinical trial coordinated by Dr. S. Halperin, Canadian Center for Vaccinology, Dalhousie University. See Appendix 9: Volker Gerdts.

Vaccine Evaluation Centre, BC Children’s Hospital

- A major contributor to IMPACT studies, which have helped shape immunization programs. For example, documented a decrease in *Haemophilus influenzae* type B from 500 cases per year to virtually none.
- Developed novel saliva tests to measure sero-prevalence of hepatitis A and Epstein Barr virus to be used for epidemiological studies.
- Developed a skin patch for immunomodulation.
- Determined that the rate of oculorespiratory syndrome following influenza vaccination declined from 2000 to 2004, but was still present (see Appendix 9: Danuta Skowronski).

Wyeth Canada

- Global company developed Prevnar, which was the first pneumococcal vaccine to be used in infants less than 2 years of age. The other vaccine in use (23 valent polysaccharide vaccine) was not very effective in inducing a memory T cell response and was not licensed for use in children. Prevnar was licensed for use in Canada in 2001. The conjugated part of the vaccine was a new technology—one lot takes one year to produce—so the vaccine has a premium price. The vaccine has been successful both medically and commercially. Has reduced invasive pneumococcal disease including reducing the rates of meningitis, pneumonia and bacteremia. Also protects adults and the elderly because unvaccinated children spread the disease to these groups. Has renewed commercial interest in vaccine development because of its commercial success.
- Global company developed Meningitec vaccine against meningococcal C disease. Vaccine given fast-track licensing in the United Kingdom, spurred by an epidemic there in 1999. It was the first vaccine against meningococcal C disease, there are two other vaccines on the market.

Appendix 9: Key accomplishments of individual vaccine researchers

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Supported by:

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Vaccine development for respiratory syncytial virus

Need: No vaccine is available for respiratory syncytial virus (RSV), a leading cause of severe respiratory disease in infants.

Goal: Utilize strategies of epitope optimization and lipid adjuvant/liposome delivery systems.

Accomplishments: Using site-directed mutagenesis of a known T helper cell epitope in the RSV G protein, it was possible to partly divorce beneficial protective from harmful inflammatory responses in candidate antigen vaccines. Further beneficial effects were realized using specific lipid adjuvants in liposome-mediated vaccine delivery.

Impact: Progress in understanding mechanisms underlying protective and inflammatory responses elicited by RSV candidate vaccines.

Publications:

Huang Y and Anderson R. 2002. Enhanced immune protection of a liposome-encapsulated recombinant respiratory syncytial virus (RSV) vaccine using immunogenic lipids from *Deinococcus radiodurans*. *Vaccine* 20:1586-1592.

Huang Y and Anderson R. 2005. Modulation of protective immunity, eosinophilia and cytokine responses by selective mutagenesis of a recombinant G protein vaccine against Respiratory Syncytial Virus (RSV). *J Virol.* 79:4527-4532.

Benoit AC, Huang Y, Maneewatchararangsri S, Tapchaisri P and Anderson R. 2007. Regulation of airway eosinophil and neutrophil infiltration by alpha-galactosylceramide in a mouse model for respiratory syncytial virus (RSV) vaccine-augmented disease. *Vaccine* 25:7754-7762.

A pilot study to determine the impact of therapeutic HIV vaccination followed by a scheduled interruption of antiretroviral therapy on HIV-specific immune function and virologic rebound in patients with prolonged viral suppression

Need: Long-term immunologic control of HIV replication may potentially be achieved if viral replication is suppressed and adequate immune recovery can occur. This, however, cannot be achieved with antiretroviral therapy (ART) alone and will require novel approaches to the enhancement of HIV-specific immune function.

Goal: To determine if, in patients with prolonged virologic suppression, therapeutic HIV vaccination (with Remune and ALVAC) followed by an interruption of ART results in a delay in viral rebound, a decrease in virologic set point and/or a slowing of CD4 decline.

Accomplishments: Vaccination with ALVAC +/- Remune delayed viral load rebound, but had no impact on viral load measured 12 weeks after ART interruption. It did, however, lengthen the time for subjects to meet pre-defined criteria to restart ART.

Impact: Although this approach did not result in clinically relevant control of viral replication, a number of vaccine recipients experienced a delay in viral load rebound and less rapid CD4 decline, potentially providing important clues for the future development of therapeutic HIV vaccines.

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Immune Response Corp.

Jonathan Angel
continued

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Ministry of Health)

Impact of CpG on vaccine antigen-specific cell-mediated immunity when administered with hepatitis B vaccine in HIV infection

Need: By improving the kinetics, magnitude and avidity of the antibody response, and the generation or augmentation of a cellular immune response (CD4⁺ T helper and CD8⁺ CTL responses) to vaccine, CpG oligodinucleotides have the potential to improve the quantity and quality of the vaccine-specific immune response.

Goal: To determine if, in HIV-infected individuals, the inclusion of CpG with hepatitis B vaccine improves the cellular immune response to the vaccine antigen.

Accomplishments: In addition to its ability to improve antibody responses, we demonstrate for the first time in humans that CpG enhances helper T cell responses to vaccine antigen in this hyporesponsive population.

Impact: This has important implications in both improving vaccine responses to currently available vaccines as well as in the development of much needed vaccines where cellular immune responses are thought to be necessary to prevent or treat disease, such as with hepatitis C, HIV and cancer.

Genomic studies of BCG vaccines

Need: Tuberculosis remains a global killer and the vaccine given at birth, BCG, has only limited efficacy.

Goal: To understand the basis for the derivation and evolution of BCG vaccines, as a means of learning why it is a partially effective vaccine.

Accomplishments: We have documented a number of mutations in BCG vaccines that serve two purposes. 1) These inform us on immunologically relevant mutations in vaccine strains, which may impact on efficacy. 2) These mutations inform us on the natural pathogenesis of mycobacterial infections by identifying processes necessary for full virulence.

Impact: There is now considerable interest in the development of new vaccines for TB.

Publications:

Behr MA, Wilson MA, Gill WP, Salamon H, Schoolnik GK, Rane S and Small P. 1999. Comparative genomics of BCG vaccines by whole genome DNA microarray. *Science* 284:1520-1523.

Mostowy S, Tsolaki A, Small P and Behr M. 2003. *In vitro* evolution of BCG vaccines. *Vaccine* 21:4270-4274.

Charlet D, Mostowy S, Alexander D, Sit L, Wilker H and Behr M. 2005. Reduced expression of antigenic proteins MPB70 and MPB83 in *Mycobacterium bovis* BCG strains due to a start codon mutation in sigK. *Mol Micro.* 56:1302-1313.

Brosch R, Gordon SV, Garnier T, Eiglmeier K, Frigui W, Valenti P, Dos Santos S, Duthoy S, Lacroix C, Garcia-Pelayo C et al. 2007. Genome plasticity of BCG and impact on vaccine efficacy. *Proc Natl Acad Sci USA* 104:5596-5601.

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MRC then CIHR

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Supported by:
CIHR

Characterization of the role of innate immunity in protection from HIV infection

Need: Natural Killer (NK) cells have the potential to control HIV infection from the earliest time in infection before the adaptive immune response has been elicited. We have shown that HIV-exposed uninfected subjects are more likely than HIV-susceptible individuals to carry certain NK cell HLA ligand pairs that have the potential to affect NK function.

Goal: The goal of the project is to characterize the activation profile of NK cells from individuals carrying NK receptor HLA ligand combinations associated with remaining uninfected despite exposure.

Accomplishments: A higher frequency to carriage of the KIR3DS1-activating NK receptor in the homozygous form and carriage of KIR3DL1 high-expression alleles with their ligand HLA Bw4 80I alleles were seen in the HIV-exposed persistently uninfected than in HIV-susceptible individuals.

Impact: Preliminary experiments support the hypothesis that having NK cells with a greater potential for activation measured by functions with anti-HIV activity (IFN- γ secretion, cytolysis) can play a role in protection from HIV infection.

Publications:

Boulet S, Sharafi S, Simic N, Bruneau J, Routy J-P, Tsoukas CM and Bernard NF. Increased proportion of KIR3DS1 homozygotes in HIV-exposed uninfected individuals. AIDS, in press.

Boulet S, Kleyman M, Kim JY, Kanya P, Sharafi S, Simic N, Bruneau J, Routy J-P, Tsoukas CM and Bernard NF. Increased frequency of KIR3DL1 subtypes with HLA-B57 in exposed uninfected compared with HIV susceptible individuals. AIDS accepted for publication.

Immunobiology of genetic vaccines

Need: Advances in molecular virology have provided an array of virus vectors that can be used to express heterologous coding sequences (transgenes) in mammalian cells *in vivo*. Since the transgenes are expressed within the context of a virus infection, their protein products are subject to immune surveillance and elicit robust cellular and humoral responses. We refer to such vectors as “genetic vaccines” since the target antigen is encoded within the genetic component of the vaccine. This approach greatly facilitates vaccine development since genes encoding putative targets can be incorporated into expression vectors with minimal knowledge of protein structure/function. Importantly, antigens from viruses such as HIV or hepatitis C (HCV) can be inserted into mildly pathogenic viruses for the purpose of immunization, eliminating the chance of inadvertently delivering the disease-causing agent to patients.

Goal: Implementation of genetic vaccination in the clinic is complicated however, by the large number of available vectors and the absence of clear criteria for vector selection. To gain greater insight into the relationship between the vaccine vector and the resultant immune response, we have chosen to compare and contrast the cellular response elicited by four distinct vaccination platforms: plasmid DNA, recombinant adenovirus, recombinant vaccinia virus and alphavirus replicons.

Accomplishments: We have investigated the relationship between the location of antigen expression, antigen presentation and T/B cell activation following immunization with these vaccines. Our studies are focused on identifying the mechanisms by which the recombinant viruses trigger adaptive immunity. Over the course of these studies, we became particularly interested in recombinant adenovirus vaccines as they have exhibited remarkable activity in pre-clinical models. While the results from early phase clinical trials using serotype 5 human adenovirus vectors were somewhat disappointing, these vectors exhibit a unique biology relative to other viruses, which offers new insight into the mechanisms of maintenance of T cell memory. Our investigations of CD8⁺ T cell and CD4⁺ T cell responses produced

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Supported by:
CIHR

by recombinant adenoviruses discovered that although these viruses do not replicate, they elicit CD8⁺ T cell responses reminiscent of viruses that establish a persistent infection. We have since determined that the CD8⁺ T cell population is maintained by very low-level gene expression that persists for weeks following adenovirus infection. Although the source of antigen during this period is unknown, we have evidence to suggest that it is located in non-hematopoietic cells suggesting a novel role for non-hematopoietic cells in the maintenance of CD8⁺ T cell memory. Interestingly, this low-level gene expression does not appear to influence the CD4⁺ T cell response. We are currently investigating how the adenovirus evokes such a response (and why other vectors/viruses do not) by examining the relationship between antigen localization and timing of antigen expression in regard to the development of CD8⁺ T cell, CD4⁺ T cell and B cell responses.

Impact: Our investigations have revealed novel insights into the mechanisms of memory maintenance following vaccination.

Publications:

Yang TC, Millar J, Groves T, Zhou W, Grinshtein N, Xing Z, Wan Y and Bramson JL. 2007. On the role of CD4⁺ T cells in the CD8⁺ T cell response elicited by recombinant adenovirus vaccines. *Mol Ther.* 15:997-1006.

Yang TC, Millar J, Grinshtein N, Bassett J, Finn J and Bramson J. 2007. T cell immunity generated by recombinant adenovirus vaccines. *Expert Rev Vaccines* 6:347-356.

Yang TC, Millar J, Groves T, Grinshtein N, Parsons R, Wan Y and Bramson JL. 2006. The CD8⁺ T cell population elicited by recombinant adenovirus displays a novel partially-exhausted phenotype associated with prolonged antigen presentation that nonetheless provides long-term immunity. *J Immunol.* 176:200-210.

Grinshtein N, Yang TC, Millar J, Parsons R, Denisova G, Leitch J, Dissanayake D, Wan Y and Bramson JL. 2006. Recombinant adenovirus vaccines can successfully elicit CD8⁺ T cell immunity under conditions of extreme leukopenia. *Mol Ther.* 13:270-279.

Dayball K, Millar JB, Miller M, Wan Y and Bramson JL. 2003. *In vivo* electroporation enables plasmid vaccines to activate CD8⁺ T cells in the absence of CD4⁺ T cells. *J Immunol.* 171:3379-3384.

Development of therapeutic vaccines for cancer

Need: Cancer vaccines should provide an ideal adjuvant to current therapies since immune cells have the unique capacity to circulate and “seek out” malignant cells within the body. Genetic vaccines are highly immunogenic and can readily incorporate tumour antigen cDNAs providing a very useful tool for tumour immunotherapy. By employing genetic vaccines to augment anti-tumour immunity in the neo-adjuvant or adjuvant setting, we hope to increase disease-free survival and extend the quality of life of cancer patients receiving conventional treatments.

Goal: Our goals for this project were to: 1) increase our biological understanding of cancer vaccines through pre-clinical investigation and 2) translate these novel findings into early-stage clinical investigation.

Accomplishments: In murine models, we have observed that recombinant adenovirus vaccines are highly efficient agents for evoking immunity against cancer antigens. Interestingly, we observed that these vaccines can be administered during periods of extreme leucopenia without affecting immunogenicity demonstrating their compatibility with conventional cancer treatments, like chemotherapy and radiation. We have also found that genetically-modified dendritic cells provide a robust platform for immunization against cancer antigens. Interestingly, the dendritic cell vaccines appear to engage separate pathways from the recombinant adenovirus vaccines. While direct immunization with recombinant adenovirus evokes robust anti-tumour CD8⁺ T cell responses, the dendritic cell vaccines elicit greater CD4⁺ T cell immunity and a unique population of anti-tumour NK cells. Another area of interest to my laboratory is the application of xenoimmunization to cancer vaccination where homologous proteins from different species are used for immunization. In principle, subtle non-conserved changes in protein sequence can give rise to

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continued

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Alliance, CANVAC.

heteroclitic epitopes that elicit T cells cross-reactive towards both the native and “xeno” antigen. To better understand the mechanisms underlying xenoimmunization, we have also employed the model melanoma antigen, dopachrome tautomerase (DCT a.k.a. TRP-2) as a model antigen due to its high degree of immunogenicity. Identification of T cell epitopes in DCT revealed a novel mechanism of action whereby CD4⁺ T cells responsive to heteroclitic epitopes within the xenoantigen can elicit effector CD8⁺ T cells specific epitopes within the native antigen. Further investigation of the CD4⁺ T cell response to DCT also revealed that the effector epitopes recognized by anti-tumour CD4⁺ T cells are generated through post-translational modification of DCT suggesting a novel pathway by which these CD4⁺ T cells may escape negative selection in thymus. An even more exciting finding relates to our recent discovery that the mechanisms by which CD4⁺ T cells mediate anti-tumour destruction and auto-immune pathology can be separated along the STAT-4/STAT-6 signalling axis. This recent result suggests that it should be possible to develop a vaccine that will selectively destroy tumour tissue without affecting healthy tissues. Our current work is targeted at further characterizing this process and testing its limits. Given the success of dendritic cell vaccines in pre-clinical models, we have been working with our colleagues at McMaster (Yonghong Wan, Ronan Foley, Bindi Dhesy, Graeme Fraser, Mark Levine) to evaluate dendritic cell vaccines in early phase human trials. We have successfully completed a Phase I/IIa trial in melanoma demonstrating the feasibility of this approach and we are in the midst of a similar trial for breast cancer. We have recently received additional support for these early phase translational investigations through research grants from the National Cancer Institute of Canada and the Ontario Institute for Cancer Research. These new funds will be directed at supporting a research program that links multiple centres across Ontario and Canada. Through these programs, we will continue to advance our prototype vaccines and evaluate novel platforms for cellular vaccination, including B cells and bone marrow stromal cells (in collaboration with Dr. David Spaner at Sunnybrook Health Sciences Centre and Dr. Jacques Galipeau at McGill University).

Impact: Based on pre-clinical and clinical efforts, we are now positioned to develop a clinical program testing different vaccine compositions to optimize the utility of these novel agents in standard clinical practice.

Publications:

Mossoba M, Walia JS, Rasaiah VI, Buxhoeveden N, Head R, Ying C, Foley JE, Bramson JL, Fowler DH and Medin J. 2008. Tumor protection following vaccination with low doses of lentivirally transduced DCs expressing the self-antigen erbB-2. *Mol Ther.* 6:607-17.

Luketic L, Delanghe J, Frotten E, Yang P, Bramson J and Wan Y. 2007. Antigen presentation by exosomes released from peptide-pulsed dendritic cells is not suppressed by the presence of active CTL. *J Immunol.* 179:5024-5032.

Kianizad K, Marshall LA, Grinshtein N, Bernard D, Beermann F, Zhang S, Wan Y and Bramson JL. 2007. Elevated frequencies of self-reactive CD8⁺ T cells following immunization with a xenoantigen is due to the presence of heteroclitic CD4⁺ T cell epitopes. *Cancer Res.* 67:6459-6467.

Lane C, Leitch J, Tan X, Hadjati J, Bramson JL and Wan Y. 2004. Vaccination-induced autoimmune vitiligo is a consequence of secondary trauma to the skin. *Cancer Res.* 64:1509-1514.

Wan Y-H, Bramson JL, Pilon A, Zhu Q and Gauldie J. 2000. Genetically modified dendritic cells prime auto-reactive T cells through a pathway independent of IL-12 and CD40: Implications for cancer vaccines. *Cancer Res.* 60:3247-3253.

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continued

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Economics of Infectious
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**Modeling the potential effectiveness and cost-effectiveness of
HPV vaccination and screening in Canada**

Need: With promising efficacy results from randomized clinical trials of candidate prophylactic HPV vaccines and the availability of new screening paradigms (e.g. HPV testing), policy makers must make decisions regarding the optimal strategies in reducing HPV infection and disease in the context of scarce health-care resources (i.e. identify the most effective and cost-effective strategies).

Goal: The aims of the project are to: 1) Develop and validate mathematical models of HPV transmission, infection (types 16, 18 and other Low Risk and High Risk types) and disease (genital warts, CIN, cervical cancer), including screening and vaccination, 2) Estimate the effectiveness and cost-effectiveness of HPV vaccination and screening.

Accomplishments: We developed a mathematical model of HPV vaccination. Our results suggested that vaccinating adolescent girls against HPV was likely to be cost-effective. However, unless screening was modified, the treatment costs saved through vaccination would be insignificant compared to the cost of HPV immunization. Using our model, we also estimated that the number needed to vaccinate to prevent an episode of genital warts was 8 and a case of cervical cancer was 324.

Impact: Our findings are currently part of the overall evidence base used to inform decision-making regarding HPV vaccination in Canada. We are currently developing a new complex individual-based model based. The model will allow us to investigate and mimic the impact of various screening algorithms (e.g. HPV triage) at the individual level, by tracking/simulating each woman's screening history. Furthermore, the model will be dynamic and therefore the herd-immunity impact of various vaccination strategies (e.g. women only, women and men) can be measured. The aim of future research is to identify integrated screening and HPV vaccination strategies that optimize the effectiveness and cost-effectiveness of cervical cancer prevention.

Publications:

Brisson M, Van de Velde N, Boily MC and De Wals P. 2007. Estimating the Number Needed to Vaccinate to Prevent HPV Related Disease Mortality. CMAJ 177:464-468.

Brisson M, Van de Velde N, Boily MC and De Wals P. 2007. The Potential Cost-Effectiveness of Prophylactic Human Papillomavirus Vaccines in Canada. Vaccine 25:5399-408.

Van de Velde N, Brisson M and Boily MC. 2007. Modelling Human Papillomavirus Vaccine Effectiveness: Quantifying the Impact of Parameter Uncertainty. Am J Epidemiol. 165:762-775.

Modeling the natural history of varicella-zoster-virus and the effectiveness and cost-effectiveness of varicella vaccination

Need: The project was initiated to provide decision makers with projections regarding the effectiveness and cost-effectiveness of varicella vaccination in Canada and the United Kingdom.

Goal: The aim of the research project was to develop and apply a dynamic mathematical model of varicella- zoster-virus transmission to predict the effectiveness and cost-effectiveness of different vaccination strategies in Canada and the United Kingdom.

Accomplishments: Two major accomplishments/outcomes came out of our research project. 1) We were the first to present strong epidemiological evidence that confirmed the hypothesis that exposure to varicella boosts immunity to zoster. That is, that exposure to varicella protects against zoster. 2) We estimated, using complex dynamic models, the effectiveness and cost-effectiveness of routine childhood varicella vaccination. We were the first to include the impact of vaccination on zoster incidence. Results showed that the cost-effectiveness of varicella vaccination was dependant on whether or not it increased zoster incidence.

Marc Brisson

continued

Supported by:

Before 2007, Health Canada (20%), FRSQ/FCAR health research (30%), United Kingdom Medical Research Council (50%)
Since 2007, Canada Research Chairs (Title: Mathematical Modeling and Health Economics of Infectious Diseases), Canada Foundation for Innovation (Infrastructure for Mathematical Modeling and Health Economics of Infectious Disease Control Interventions)

Impact: Our findings had and still have major implications for varicella vaccination: by reducing varicella cases (and thus the opportunity of exposure to VZV), mass infant immunization could increase the incidence of zoster in individuals who have not been vaccinated. The study supported a re-evaluation of varicella vaccination taking into account its possible impact on zoster. The research was selected as one of the 100 top Science stories of 2002 by the editors of Discover magazine. The research was also instrumental in recommendations regarding the routine administration of varicella vaccination in Canada, Australia and Europe. Furthermore, our research has been an impetus for long-term surveillance of zoster in the United States, where routine childhood varicella vaccination was introduced in 1995.

Publications:

Brisson M and Edmunds WJ. 2003. Varicella Vaccination in England and Wales: Cost-utility analysis. *Arch Dis Child*. 88:862-869.

Brisson M and Edmunds WJ. 2003. Economic evaluation of vaccination programmes: The impact of herd-immunity. *Med Decis Making* 23:76-82.

Brisson M, Gay NJ, Edmunds WJ and Andrews NJ. 2002. Exposure to Varicella Boosts Immunity to Herpes-zoster: Implications for mass vaccination against chickenpox. *Vaccine* 20:2500-2507.

Brisson M and Edmunds WJ. 2002. The cost-effectiveness of varicella vaccination in Canada. *Vaccine* 20:1113-1125.

Brisson M, Edmunds WJ, Gay NJ, Law B and De Serres G. 2000. Modelling the impact of immunization on the epidemiology of varicella zoster virus. *Epidemiol Infect*. 125:651-669.

Development of a *Chlamydia* T cell vaccine based on dendritic cell immunoproteomics

Need: Often asymptomatic, sexually transmitted *Chlamydia trachomatis* infects over 92 million people per year globally, is a leading cause of pelvic inflammatory disease (PID) that results in 2-3 million annual cases of infertility and is linked to 60,000 maternal deaths per year due to ectopic pregnancy. With control programs failing, the development of a safe and effective *Chlamydia* vaccine would represent a fundamental breakthrough in global health as well as saving in excess of \$13.5 billion per year world wide in treatment costs. In this proposal a novel immunoproteomic approach is described based on identifying *Chlamydia* peptides capable of producing protective cellular immunity that shows great promise towards the development of a *Chlamydia* vaccine.

Goal: Using mass spectrometry, the first specific aim is to discover the identity of additional *Chlamydia* peptides eluted from MHC class I and class II molecules expressed on the surface of *Chlamydia*-infected dendritic cells. Our second specific aim is to uncover the immunological significance of *Chlamydia* MHC binding peptides. Based on the antigens we know, and others we plan to uncover in this study, our proposed research to induce cell-mediated immunity in animal models is a major step in the development of a safe and effective *Chlamydia* vaccine for humans.

Accomplishments: Inspired by the global magnitude of need for a *Chlamydia* vaccine and propelled by recent advances in proteomic technology, genomics and knowledge of *Chlamydia* immunology, we have identified novel antigens critical to the design of an effective *C. trachomatis* vaccine. We believe that we have achieved a breakthrough by using immunoproteomics to identify T cell antigens that are expressed in *Chlamydia*-infected dendritic cells – achieved in part because we have access to the latest generation of mass spectrometry capable of detecting peptides at the subfemtomolar level.

Robert C Brunham
Provincial Executive
Director
BC Centre for Disease
Control

Supported by:

NIH Operation Grant (50%),
CIHR proof of principle grant
(10%), Genome BC (10%),
Michael Smith Foundation
(5%), The Provincial Health
Services Authority of BC/
BCCDC (25%).

Robert C Brunham
continued

Supported by:
CIHR, BC Ministry of Health

Impact: This project will accelerate progress toward a *Chlamydia* vaccine, which will be a major medical achievement for global health.

Publications:

Karunakaran KP, Rey-Ladino J, Stoykov N, Berg K, Shen C, Jiang X, Gabel BR, Yu H, Foster LJ and Brunham RC. 2008. Immunoproteomic discovery of novel T cell antigens from the obligate intracellular pathogen *Chlamydia*. *J Immunol.* 180:2459-65.

Rey-Ladino J, Jiang X, Gabel BR, Shen C and Brunham RC. 2007. Survival of *Chlamydia muridarum* within Dendritic Cells. *Infect Immun.* 75:3707-3714.

HPV vaccine implementation in British Columbia

Need: In keeping with the Erickson/deWals principles, there is a need to examine a variety of elements beyond vaccine efficacy when implementing a new vaccine program, and for policy makers to have relevant provincial data as the foundation for these decisions.

Goal: For the province of British Columbia to have an evidence-based foundation for decision making regarding the implementation of the HPV vaccine program.

Accomplishments: Prepared a comprehensive, evidence-based platform for decision making on the HPV vaccine, which included province-specific HPV prevalence rates, parental attitudes to the vaccine, mathematical modeling and cost effectiveness analysis of the HPV vaccine. As part of our ongoing population-based evaluation of the HPV vaccine, we hope to be monitoring population-based HPV-type-specific prevalences in partnership with the HPV FOCAL trial and the immunologic response to a two vs three dose HPV vaccine schedule.

Publications:

Ogilvie GS, Remple VP, McNeil SA, Marra F, Naus M, Pielak KL, Ehlen TG, Dobson SR, Patrick DM and Money DM. 2007. Parental intention to have daughters receive the human papillomavirus vaccine. *Can Med Assoc J.* 177:1506-12.

SARS vaccine

Need: Rare disease with very high mortality and no anti-viral drugs available.

Goal: To develop a series of vaccines based on various strategies and compare efficacy in inducing antibody and preventing disease in an animal model.

Accomplishments: Whole killed virus, adenovirus vectored and binding subunit vaccines were developed. The former two were tested in a ferret and mouse model. Whole killed virus vaccine was effective in preventing virus growth and pathology.

Impact: Candidate vaccines are available. Proof of principle has been achieved. Requires production in GMP environment.

Publications:

Finlay B, See RH and Brunham RC. 2004. Rapid response research to emerging infectious diseases: lessons from SARS. *Nature Reviews Microbiology* 2:602-607.

Robert C Brunham

continued

Supported by:

CIHR, BC Ministry of Health

David Bundle
Professor of Chemistry and
Director of the Ingenuity
Centre for Carbohydrate
Science
University of Alberta

Supported by:

CIHR, NSERC, NIH, Alberta
Ingenuity, Alberta Heritage
Foundation for Medical
Research

***Candida albicans* conjugate vaccines: Evaluation of synthetic beta-mannan oligosaccharides conjugated to immunogenic carriers in rabbit and mouse models of experimental candidiasis**

Need: Individuals scheduled to receive abdominal surgery, transplantations, including bone marrow, kidney or heart, immunosuppressive cancer therapy, as well as AIDS patients and those exposed to long-term hospitalization are at high risk of developing life threatening infections due to *Candida albicans*. Treatment by anti-fungal drugs is attended by problems such as toxicity and antibiotic resistance. Immunological prevention of candidiasis by immunization with synthetic conjugate vaccines is proposed as a low risk approach to prevent infection and reduce the cost of current therapy.

Goal: Aim 1: Design and employ a viable and flexible strategy to synthesize 100-500 mg of native trisaccharide epitope functionalized with a multifunctional tether, which permits covalent coupling to an immunogenic carrier protein by at least two chemically distinct coupling methods, without inducing a dominant antibody response to tether elements. Aim 2: Develop and optimize two or three chemical coupling strategies to create the critical trisaccharide protein linkage in a highly convergent and efficient process that conserves precious oligosaccharide epitope. Aim 3: Introduce catabolically stable glycosyl elements linked via a sulphur atom that mimic the native O-linked residue, and which by virtue of their resistance to hydrolytic enzymes induce a more robust beta-mannan specific response when presented as conjugate vaccines. Aim 4: Establish that trisaccharide conjugate vaccines can induce protective immunity in mice against *Candida* by stimulating a secondary immune response with antibodies of the appropriate IgG subclass. Aim 5: Investigate the optimal choice of carrier protein to achieve aim 4 and to ensure that this response may be generated by only two injections given

without adjuvant or with adjuvants that are approved for use in human subjects. Aim 6: Immunize mice and rabbits according to the above protocols and perform live *Candida* challenge experiments to establish that beta-mannan responses induced by synthetic conjugate vaccines afford protection in animal models of disseminated candidiasis.

Accomplishments: Vaccine and diagnostic conjugates were prepared by conjugation of synthetic trisaccharide hapten to tetanus toxoid and bovine serum albumin via an adipic acid tether. Vaccine efficacy was evaluated in a disseminated candidiasis rabbit model. New Zealand white rabbits were immunized on days 0 and 21 with an alum suspension of trisaccharide- tetanus toxoid conjugate vaccine. To induce disseminated candidiasis, immunosuppressed rabbits were challenged by i.v. inoculation with a clinical strain of *C. albicans*. The experiment was terminated 8 days following the challenge and a *Candida* colony count was performed on the liver, spleen, kidneys and lungs. Significant reduction of viable *Candida* cells was observed in kidneys and liver as compared to control animals (injected with tetanus toxoid).

Impact: Patents were filed and the intellectual property was licensed to a spin-off company, TheraCarb Inc. TheraCarb subsequently sublicensed the technology to a US company for co-development of a vaccine.

Publications:

Nitz M, Ling C-C, Otter A, Cutler JE and Bundle DR. 2002. The unique solution structure and immunochemistry of the *Candida albicans* b-1,2-mannopyranan cell wall antigen. *J Biol Chem.* 277:3440-3446.

Wu X and Bundle DR. 2005. Synthesis of glycoconjugate vaccines for *Candida albicans* using novel linker methodology. *J Org Chem.* 70:7381-7388.

David Bundle
continued

David Bundle

continued

Bundle DR, Rich JR, Jacques S, Yu HN, Nitz M and Ling C-C. 2005. Thio-oligosaccharide conjugate vaccines evoke antibodies specific for native antigens. *Angew Chem Int Ed.* 44:7725-7729.

Dziadek S, Jacques S and Bundle DR. 2008. A novel linker methodology for the synthesis of tailored conjugate vaccines composed of complex carbohydrate antigens and specific TH-cell peptide epitopes. *Chem Eur J.* 14:5908-5917.

Xin H, Dziadek S, Bundle D R and Cutler J. 2008. Synthetic glycopeptide vaccines combining β -mannan and peptide epitopes induce protection against candidiasis. *Proc Natl Acad Sci (USA)*. (in press).

Molecular epidemiology and surveillance network for human papillomavirus (HPV) in Manitoba women - A pilot study

Need: Canadian governments are investing time and money in vaccinating a large cohort of young women with the new HPV vaccines. The magnitude of the impact of this vaccination program, as well as its value, remains controversial. It is important to set up the infrastructure to be able to assess the efficiency of the program.

Goal: 1. Determine the feasibility of collecting an HPV sample, and its acceptability by the health-care providers from three community clinics in Winnipeg and by the women attending these clinics. 2. Develop and test a culturally appropriate questionnaire and consent form. 3. Establish and streamline the operational details for specimen collection, transportation, and molecular testing. 4. Obtain preliminary estimates of the prevalence and distribution of common HPV types in order to fine-tune plans for the provincial survey.

Accomplishments: It was possible to develop, in collaboration with the clinics, an efficient and secure way to collect tissue samples and administer a survey. The study provides an estimate of the level of HPV infections for people living in the core of the city of Winnipeg as well as the risk factors associated with these infections.

Impact: The pilot project will be used as leverage to organize a larger surveillance study where sentinel sites will be created to monitor the impact of the vaccines in a teenager population.

Alain Demers
Epidemiologist
CancerCare Manitoba

Supported by:
CancerCare Manitoba
Foundation

Alain Demers
continued

Supported by:
Private funding

Epidemiology of genital warts, *in situ* and invasive cervical cancer and associated health care resources utilization and costs in Manitoba

Need: In order to be able to predict the cost-effectiveness of the HPV vaccines, it is essential to be able to determine the actual costs and services associated with HPV-related diseases.

Goal: 1. Determine the epidemiology of genital warts in males and females. 2. Determine the epidemiology of cervical dysplasia, *in situ* and invasive cervical cancer. 3. Determine the utilization of health-care resources and related costs associated with the diagnosis and treatment of genital warts, cervical dysplasia, *in situ* and invasive cervical cancer.

Accomplishments: A first report has been published on genital warts. The report on cervical dysplasia as well as the cost analysis will be produced shortly.

Impact: The information will be used in a model that will estimate the impact of the HPV vaccines on the health-care system.

A controlled trial to assess the immunogenicity of a proposed pediatric dosing schedule of HPV

Need: HPV infection is a cause of cervical cancer.

Immunogenicity, safety and efficacy in the prevention of persistent infection from HPV 16 and 18 has been proven using a 3-dose regimen in adolescent and adult females using the Quadrivalent Human Papillomavirus (Q-HPV) vaccine. The intensity of the immune response is inversely proportional to age. Immunogenicity in adolescents 9-15 years of age is 1.7 – 2 times greater than in 16-26 year old vaccine recipients. Pediatric dosing studies are necessary and prudent given limited provincial funding for new biologics acquisition and programme service delivery. A reduction from an adult 3-dose HPV vaccine regimen to a pediatric 2-dose regimen will result in increased compliance to the full vaccine series and in significant savings to the health-care system both in the cost of biologics and of program delivery and administration.

Goal: Active immunization of girls 9-13 years of age for prevention of persistent infections from HPV 6, 11, 16 and 18 genotypes and related clinical outcomes (condyloma, cytological abnormalities and pre-cancerous lesions) in a cost-efficient pediatric 2-dose regimen.

Accomplishments/Outcomes: The main accomplishment was getting the study funded at all. Vaccine manufacturers are not interested in funding studies to determine whether fewer doses of their product will be satisfactory. Funding came directly from provincial governments. The recognition that funding programmatic vaccine research is important and not currently well served by traditional research funding sources will turn out to be an important outcome of this project. 825 girls in BC, Nova Scotia and Quebec were recruited between August 2007 and February 2008 and the study is on-going.

Simon Dobson
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Vaccine Evaluation Centre,
BC Children's Hospital
University of British
Columbia

Supported by:

BC Government (\$1.8 million 78%) administered through the Michael Smith Health Research Foundation with additional money for field work at their respective sites by the Governments of Nova Scotia (\$250,000 11%) and Quebec (\$250,000 11%)

Simon Dobson
continued

Supported by:
Chiron Corporation
(now Novartis)

Anticipated or realized impact of research project:

Proving the non-inferiority in immunogenicity of 2 doses in pre-teens with 3 doses of HPV vaccine in young adult women would allow provinces to consider 2-dose schedules which in turn would allow more girls to receive HPV vaccine for a fixed allocation of money.

A Phase II, randomized, open label, controlled, multicentre study to evaluate the safety, immunogenicity and induction of immunological memory after two or three doses of Chiron meningococcal ACWY conjugate vaccine administered to healthy infants at 2, 3, 4 or 2, 4, 6 months of age

Need: Meningococcus bacteria consists of several different serogroups that can cause a serious form of disease called meningitis (infection around the surface of the brain). It is rare, but can be life threatening and mostly affects babies and young children. The lowest antibody levels are found in infants between 6 months and 2 years of age. At this time there is only one vaccine to offer protection to babies against the serogroup C bacteria. It is routinely given at 1 year of age in Canada. This new vaccine contains protection against A, C, W and Y and has been made in a similar way to the routinely used meningococcal C vaccine. This new vaccine has been tested in adults and toddlers and proven to be safe, well tolerated and immunogenic.

Goal: To evaluate the safety, immunogenicity and induction of immunological memory of a new meningococcal vaccine. This new vaccine has been developed to protect babies not only against serogroup C, but also against meningitis caused by three other members of the meningococcal family known as serogroup A, W and Y. The vaccine will be immunogenic in either the 2-dose or 3-dose regime and the vaccine will be safe to administer to infants along with their routine immunizations.

Accomplishments: The vaccine was satisfactorily immunogenic in infants.

Impact: If and when the vaccine is licensed in Canada, it would be the first such vaccine in Canada available to be given to infants under the age of 2 years.

Publications:

Snape MD, Perrett KP, Ford KJ, Pace D, Ly-Mee Y, Langley JM, McNeill S, Dull PM, Ceddia F, Anemona A, Halperin SA, Dobson S and Pollard AJ. 2008. Immunogenicity of a tetravalent meningococcal glycoconjugate vaccine in infants: a randomized controlled trial. *JAMA*. 299:173-184.

Simon Dobson
continued

Roy Duncan
Professor
Canadian Centre for
Vaccinology
Dalhousie University

Supported by:

CIHR operating, CIHR proof
of principle, NSERC Strategic

**Development of an intracellular antigen delivery system
based on fusogenic liposomes.**

Need: Current means for antigen delivery inside target cells need to be improved in order to stimulate more robust cytotoxic lymphocyte (CTL) responses to subunit antigens.

Accomplishments: We determined that liposomes carrying the reovirus p14 fusion-associated small transmembrane (FAST) protein fuse with the plasma membrane of numerous cell types, bypassing the inefficient and degradative endocytic pathway for liposome uptake and resulting in a >20-80 fold increase in intracellular delivery of entrapped liposome cargo (i.e. small molecules, plasmid DNA, pro-apoptotic peptides). We are currently determining whether the FAST-liposomes, in combination with different adjuvants and immune modulators, can be used to induce a balanced Th1/Th2 response while stimulating a robust CTL response.

Impact: The development of an efficient intracellular antigen delivery platform capable of carrying a diversity of antigens and adjuvants would have significant impact on enhancing cell mediated immunity, improving the efficacy of existing and new vaccines.

Publications:

Salsman J, Top D, Barry C and Duncan R. 2007. A virus-encoded cell-cell fusion machine dependent on surrogate adhesins. *PloS Pathogens* 4:e1000016.

Mader JS, Richardson A, Salsman J, Top D, de Antueno R, Duncan R and Hoskin DW. 2007. Bovine lactoferricin causes apoptosis in human T-leukemia cells by directly targeting mitochondria subsequent to cell membrane permeabilization. *Exp Cell Res.* 313:2634-2650.

Corcoran JA, Salsman J, de Antueno R, Touhami A, Jerricho MH, Clancy EK and Duncan R. 2006. The p14 fusion-associated small transmembrane (FAST) protein effects membrane fusion from a subset of membrane microdomains. *J Biol Chem.* 281:31778-31789.

Top D, de Antueno R, Salsman J, Corcoran J, Mader J, Hoskin D, Jerricho M and Duncan R. 2005. Liposome reconstitution of a minimal protein-mediated membrane fusion machine. *EMBO J.* 24:2980-2988. (Editor's choice, *Science* 309:1155).

Roy Duncan
continued

Brett Finlay
Professor
University of British
Columbia

Supported by:
BC Government, CIHR III,
MSHRF

Develop SARS vaccine (Sars Accelerated Vaccine Initiative (SAVI))

Need: SARS threat.

Goal: Rapidly develop prototype SARS vaccines using whole killed virus, adenovirus expressing SARS spike protein; and recombinant spike protein.

Accomplishments: Made all three vaccines, tested in two relevant animal models, several papers published.

Impact: Developed a new way of doing rapid response vaccine development science. If SARS reappears, can consider developing vaccines further.

Publications:

Zakhartchouk AN, Sharon C, Satkunarajah M, Auperin T, Viswanathan S, Mutwiri G, Petric M, See RH, Brunham RC, Finlay BB, Cameron C, Kelvin DJ, Cochrane A, Rini JM and Babiuk LA. 2007. Immunogenicity of a receptor-binding domain of SARS coronavirus spike protein in mice: implications for a subunit vaccine. *Vaccine* 25:136-143.

See RH, Zakhartchouk AN, Petric M, Lawrence DJ, Mok CP, Hogan RJ, Rowe T, Zitzow LA, Karunakaran KP, Hitt MM, Graham FL, Prevec L, Mahony JB, Sharon C, Auperin TC, Rini JM, Tingle AJ, Scheifele DW, Skowronski DM, Patrick DM, Voss TG, Babiuk LA, Gauldie J, Roper RL, Brunham RC and Finlay BB. 2006. Comparative evaluation of two severe acute respiratory syndrome (SARS) vaccine candidates in mice challenged with SARS coronavirus. *J Gen Virol.* 87(Pt 3):641-650.

Finlay BB, See RH, Brunham RC. 2004. Rapid response research to emerging infectious diseases: lessons from SARS. *Nat Rev Microbiol.* 2:602-607.

Develop non-typhoidal *Salmonella* vaccine with secreted proteins

Need: Significant need for poultry vaccine, no human non-typhoidal vaccine.

Goal: Induce *Salmonella* virulence factors that are secreted proteins, use as supernatant vaccine.

Accomplishments: Have identified conditions to induce optimal protection in mice and chickens. Five-log decrease in mouse model.

Impact: Moving towards poultry vaccine. Need non-typhoidal *Salmonella* vaccine in developing countries.

Develop O157 *E. coli* cattle vaccine

Need: Outbreaks of *E. coli* O157 like Walkerton.

Goal: Vaccinate cows to protect against carriage and shedding.

Accomplishments: Developed vaccine, works well. Further developed by Bioniche, have received initial approval for Canada, working on US.

Impact: Significantly decrease *E. coli* O157 disease in humans.

Publications:

Potter AA, Klashinsky S, Li Y, Frey E, Townsend H, Rogan D, Erickson G, Hinkley S, Klopfenstein T, Moxley RA, Smith DR and Finlay BB. 2004. Decreased shedding of *Escherichia coli* O157:H7 by cattle following vaccination with type III secreted proteins. *Vaccine* 22:362-369.

Horne C, Vallance BA, Deng W and Finlay BB. 2002. Current progress in enteropathogenic and enterohemorrhagic *Escherichia coli* vaccines. *Expert Rev Vaccines* 1:483-493.

Brett Finlay

continued

Supported by:

Awarded a CIHR PoP grant for further development. All the original work was funded by CIHR III Team grant as part of Food and Water Safety Initiative.

Supported by:

MRC, CIHR, CBDN

Yves Fradet
Uro-oncologist at CHUQ
Hospital and
Head of Surgery
Department
Laval University

Supported by:
2005-2008 CIHR, 2008-
2011 CIHR

Cancer-testis antigen-based immunotherapy of bladder cancer

Need: Bladder cancer is the fifth most common cancer in the Western world. Most of these tumours are transitional cell carcinomas and about 75% are superficial. Although most of these tumours present a good prognosis, they are associated with a high rate of recurrence since more than 60% will recur after surgery, and a significant proportion of these recurrences (5-25%) will progress toward a more aggressive disease. Superficial bladder cancer thus represents a unique opportunity to develop and test cancer vaccines that could be used after surgery to prevent tumour recurrence, in an ideal setting of low tumour burden. Moreover, we hypothesize that this type of cancer could respond well to specific immunotherapy because it is one of the rare cancers to show clinical response after intravesical instillation of bacillus Calmette-Guérin (BCG), a nonspecific immunotherapy treatment.

Goal: Cancer-testis antigens (CTAs) possess several features of ideal targets for cancer immunotherapy. They are expressed in a large variety of tumours but their expression in normal tissues is restricted to gametogenic tissues, which are immunoprivileged because of their lack or low expression of HLA molecules. Moreover, several studies have shown the existence of natural cellular and humoral responses against some CTAs indicating that they are relevant targets for cancer immunotherapy. The objective of the study is to develop a bladder cancer immunotherapy that would be more efficient in preventing recurrence of the superficial tumours than the current BCG treatment.

Accomplishments: Reverse-transcriptase polymerase chain reaction analysis of the expression of a series of CTAs in a panel of bladder tumours, showed that mRNAs of the MAGE-A family were the most frequently expressed with 65% of

bladder tumours expressing them at a level above that found in normal urothelium. We further characterized the expression of the various members of the MAGE-A family and found that MAGE-A9 mRNA was the MAGE-A mRNA most frequently expressed in these tumours. Monoclonal antibodies against MAGE-A9 have been produced and used to characterize the expression of this antigen in fixed and paraffin-embedded bladder tumours as well as in tumours originating from various organs as MAGE-A9 expression has been poorly characterized to date.

Impact: This research brings together several scientists who form a multidisciplinary team (urologists, molecular biologists and immunologists). This research could lead to the development of a cancer vaccine that could be used to prevent the recurrence of bladder tumours after surgery or even the occurrence of bladder tumours in individuals at risk.

Publications:

Fradet Y, Picard V, Bergeron A and LaRue H. 2006. Cancer-Testis Antigen Expression in Bladder Cancer. *Progrès en Urologie*. 16:421-428.

Picard V, Bergeron A, LaRue H and Fradet Y. 2007. MAGE-A9 mRNA and Protein Expression in Bladder Cancer. *International Journal of Cancer* 120:2170-2177.

Yves Fradet

continued

Eduardo L. Franco
Professor
McGill University
Montreal

Supported by:

GSK for the trial. My research on cervical cancer at McGill has been funded by CIHR, NIH and NCIC (early studies).

Assisted GSK during its clinical development phase for an HPV vaccine

Need: Although screening for cervical cancer has been shown to reduce rates of this disease in most developed countries, it has failed to produce the expected dividends in developing countries. An HPV vaccine can prevent most cervical precancerous lesions caused by the vaccine-target HPV types.

Goal: To assess the efficacy of a bivalent VLP-L1 vaccine against HPV types 16 and 18 in a randomized controlled trial.

Accomplishments: Dr Franco was the co-lead investigator in the 2 papers that reported the results of this vaccine.

Impact: Selected by The Lancet among the most important contributions of 2006 in the medical field. Dr Franco has been awarded the O. Harold Warwick prize of cancer control research of 2004 (given in 2005) for his work on cervical cancer prevention.

Publications:

Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. 2004. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomized controlled trial. *Lancet* 364:1757-1765.

Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, et al. 2006. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomized control trial. *Lancet* 367:1247-1255.

Establishment of the RE Fitzhenry vector facility at McMaster University

Need: Canada has no readily accessible facility that can be used to manufacture small lots of clinical grade vectors at a GMP level for vaccine trials in Phase I or II. Preparations intended for human use previously needed to be tendered outside the country at very high costs.

Accomplishments: We established the RE Fitzhenry Vector Facility with generous support from CFI, OIT and benefactor donations. This is a 3000 sq ft purpose-built and dedicated laboratory with extensive controls, clean rooms and bottling capacity to manufacture vector vaccines suitable for clinical trials in 50 to 100 patients. The facility is managed by Dr. Maria Medina and is GMP compliant.

Impact: The Vector Facility is fully functional and capable of manufacturing small-scale clinical lots within 4 to 6 months of initiating the process. Initially set up to manufacture GMP lots of adenovirus vectors, it is also being adapted for VSV vectors and AAV vectors for vaccine use. We have already produced a clinical lot of adenovirus vector-based vaccine for TB clinical trials to be carried out by Drs. Zhou Xing and Fiona Smaill at McMaster in early 2009.

Publications:

Medina MFC, Sankar U, Xing Z, Smaill F and Gauldie J. 2008. Clinical production of an adenovirus-based tuberculosis vaccine for a Phase I safety trial. *Molecular Therapy* 16:S107.

Medina MFC, Sankar U, Rudy J and Gauldie J. 2007. Commissioning of an aseptic processing area for clinical production of adenoviral vectors. *Molecular Therapy* 15:S121.

Medina MFC, Rudy J, Sankar U, Chong D, Foley R and Gauldie J. 2006. Production of adenoviral vectors in an academic cGMP facility. *Molecular Therapy* 13:S121.

Jack Gauldie
Professor of Pathology and
Director of the Centre for
Gene Therapeutics
McMaster University

Supported by:
CFI, OIT, RE Fitzhenry

Jack Gauldie
continued

Supported by:

CIHR, NCIC, CANVAC – NCE,
CBCRA and OICR

**Dendritic cell-based genetic vaccines for breast cancer,
chronic lymphocytic leukemia and prostate cancer**

Need: Awakening the host immune response to the presence of tumour cells requires potent stimulation of antigen-specific immunity, both antibody and cellular systems, in particular, the CD4 and CD8 cells of the immune system. For the most part, the tumour-associated antigens to be targeted are either self antigens expressed at high levels, or modestly modified self antigens, in either case, the aspect of self-tolerance needs to be considered and neutralized, preferably in an antigen-specific manner. Dendritic cells are the most potent of the antigen presenting cells of the immune system and can be cultured and expanded from either bone marrow or peripheral blood precursor cells through *in vitro* manipulation. These cells can be matured and loaded with antigen specificity, either through specific epitope peptides, or through gene transfer of tumour antigens either by viral vector exposure or transfer of tumour RNA. This “personalized” approach to vaccine development is likely to be restricted to “therapeutic” vaccines and unique situations where mass immunization (prophylactic) is not feasible.

Accomplishments: We developed a well managed clinical trial system for cancer vaccines at the Juravinski Cancer Centre and the DeGroot Centre at McMaster with Ronan Foley, Bindi Dhesy-Thind, Graeme Frazer, Richard Tozer, Yonghong Wan, Jonathan Bramson and Mark Levine. We have developed routine approaches to isolate and expand human dendritic cells with pheresis of patients with cancer and load these with antigens characteristic of tumours.

We developed a xeno-antigen approach for the expression of rodent Her2 in human dendritic cells isolated from patients with breast cancer and initiated a “First in Man” Phase I/II trial using this dendritic cell vaccine with xeno-Her2 antigen. This trial is compared with a trial in which the patients were administered the vector expressing rodent Her2 alone.

We also developed approaches using dendritic cells isolated and expanded from patients with Chronic Lymphocytic Leukemia and loaded these with RNA isolated from the patients' CLL cells. We have conducted a 10 patient trial of "First in Man" using RNA-loaded dendritic cells in CLL.

We have developed a dendritic cell-based vaccine of cells loaded with Muc1 peptides for therapeutic vaccine trials in prostate cancer which is starting accrual in June 2008. These trials are continuing and patient monitoring for immune reactions are being followed through interaction with Rafick Sekaly in Montreal.

Impact: These trials have shown the feasibility and safety of using cell-based genetic vaccines for therapeutic vaccine interventions. We have preliminary data showing immune responses in patients receiving the dendritic cell-based vaccine compared to the vector alone. A very successful infrastructure has been developed in Hamilton for conducting dendritic cell-based vaccine trials and cell processing.

Publications:

Suresh K, Rodriguez-Lecompte JC, Gauldie J and Foley R. 2005. Recent advances in immunotherapy of B-CLL using *ex vivo* modified dendritic cells. *Hematology* 10:189-203.

Suresh K, Fraser G, Scheid E, Leber B, Gauldie J and Foley R. 2006. Generation of *in vitro* B-CLL specific HLA class I restricted CTL responses using autologous dendritic cells pulsed with necrotic tumour lysate. *Leuk Lymphoma* 47:297-306.

Trial Protocols:

A Phase I Study Investigating Multiple Injections of Autologous CD34⁺ Derived Dendritic Cells Transduced with an Adenovirus Expressing Rat Her-2/neu in Patients with Metastatic Breast Cancer.

Jack Gauldie
continued

Jack Gauldie
continued

Supported by:
CIHR and CANVAC - NCE

A Phase I/II Study Evaluating the Safety and Efficacy of Vaccination with Autologous Dendritic Cells Loaded with Synthetic Tn-MUC1 Peptide in Patients with Non-Metastatic Androgen Independent Prostatic Adenocarcinoma.

A Phase I/II Study Investigating Multiple Injections of CLL-DCV01 in Patients with Previously Treated B-cell Chronic Lymphocytic Leukemia.

Definition of immune response at the mucosa in response to vaccine delivery

Need: Many vaccine developments are aimed at providing protection for individuals against organisms that regularly use the nasopharyngeal, gastrointestinal, respiratory or genitourinary mucosa as the route of entry. Thus, most “conventional” approaches to vaccine delivery do not provide adequate protection at the mucosa, even though there are potent responses detected in the systemic (lymphatic and plasma) components. This is particularly true for aspects of cellular immunity. There is a need to better understand the content and dynamics of the innate and adaptive immune response at the mucosa and develop immunization routes that provide maximum protection at these sites.

Accomplishments: We developed approaches to use viral vectors to target mucosa of the lung and colon, with the goal of understanding the function of the innate dendritic cell (DC) population at those tissues and stimulating the local mucosal immune response. We characterized the DCs from lung and colon and showed they differ not only from spleen, but also from each other, with markedly different expression of Toll receptors, determined by the microenvironments of the different tissues. Moreover, in comparison to systemic routes of immunization, providing the immunization priming reaction at the specific mucosal tissue site resulted in significantly greater protection against infectious virus challenge.

Impact: Many of the current approaches of delivery of vaccines fail to provide adequate protection at the mucosal surfaces where the infectious organisms enter. Mucosal specific immunization schedules will be more effective in providing protection against common organisms, such as airborne infections (influenza) and sexually transmitted diseases (Herpes and HIV).

Publications:

Takenaka S, Safroneeva E, Xing Z and Gauldie J. 2007. Dendritic cells derived from murine colonic mucosa have unique functional and phenotypic characteristics. *J Immunol.* 178:7984-793.

Zhu Q, Thomson CW, Zhang G, Stämpfli M, McDermott MR, Collins SM and Gauldie J. 2007. Eosinophilia is induced in the colon of Th2-sensitized mice upon exposure to locally expressed antigen. *Am J Physiol Gastrointest Liver Physiol.* 293:G383-390.

Zhu Q, Thomson CW, Rosenthal KL, McDermott MR, Collins SM and Gauldie J. 2008. Immunization with adenovirus at the large intestinal mucosa as an effective vaccination strategy against sexually transmitted viral infection. *Mucosal Immunology* in press.

Jack Gauldie

continued

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Supported by:
CIHR

Evaluation of vaccine candidates against leishmaniasis

Need: Leishmaniasis is a neglected disease of public health importance which affects several million people in the tropical and subtropical regions of developing countries. The World Health Organization considers the disease to be one of the most serious, epidemic-prone parasitic infectious disease of our time. There is no vaccine to prevent leishmaniasis, leaving chemotherapy the only means of treating the disease which could result in drug resistance.

Goal: The goal is to evaluate vaccine candidate antigens for their immunogenicity and their potential to elicit protective Th1 response in mouse model and also further assess their specific immune responses on samples from leishmaniasis patients.

Accomplishments: We have employed a prime-boost immunization strategy using DNA/DNA, DNA/protein and protein/protein approaches in the presence and absence of adjuvants and assessed the immunogenicity of our potential vaccine candidates in mice. We have established the Th1 response using the various approaches and have initiated protection studies against infection. We have also established collaborations with the Armauer Hansen Research Institute (AHRI) in Ethiopia to evaluate the specific immune responses against the recombinant proteins on samples from visceral and cutaneous leishmaniasis patients in established *Leishmania* endemic sites. We have encouraging results from one antigen that has been tested.

Impact: Our overall research will help in the development of antigens as affordable vaccines for leishmaniasis.

Development of novel vaccine formulations for the neonate

Need: Vaccination of the very young is highly ineffective due to the immature immune system, the bias towards a Th2 response and the interference with maternally-derived antibodies. As a consequence multiple immunizations are often required to induce protective immunity. Vaccines that can overcome some of these challenges and that work after a single shot are urgently needed.

Goal: To develop novel vaccine formulations (adjuvants) for infants that can be used at a very early age of life and that only require a single-shot immunization.

Accomplishments: Using pertussis (whooping cough) as a model disease, we were able to demonstrate that the addition of novel adjuvants and immune stimulators greatly enhanced the immune response in, and increased protection against, challenge infection in mice and pigs.

Impact: Developing platform technologies that are based on a combination of vaccine antigen and adjuvants/immunostimulators will also be applicable to other neonatal diseases and have a great impact on neonatal and early childhood health worldwide.

Publications:

Gerdts V, Littel-van den Hurk SD, Griebel PJ and Babiuk LA. 2007. Use of animal models in the development of human vaccines. *Future Microbiol.* 2:667-675.

Elahi S, Holmstrom J and Gerdts V. 2007. The benefits of using diverse animal models for studying pertussis. *Trends Microbiol.* 15:462-468.

Elahi S, Buchanan RM, Babiuk LA and Gerdts V. 2006. Maternal immunity provides protection against pertussis in newborn piglets. *Infect Immun.* 74:2619-627.

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Supported by:

CIHR, Bill and Melinda Gates Foundation, Krembil Foundation, Agriculture Development Fund Saskatchewan

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continued

Supported by:

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Elahi S, Buchanan RM, Attah-Poku S, Townsend HG, Babiuk LA and Gerdts V. 2006. The host defense peptide beta-defensin 1 confers protection against *Bordetella pertussis* in newborn piglets. *Infect Immun.* 74:2338-2352.

Elahi S, Brownlie R, Korzeniowski J, Buchanan R, O'Connor B, Peppler MS, Halperin SA, Lee SF, Babiuk LA and Gerdts V. 2005. Infection of newborn piglets with *Bordetella pertussis*: a new model for pertussis. *Infect Immun.* 73:3636-645.

Maternal immunization against pertussis

Need: There is great need to provide better means of control for neonatal infections such as pertussis.

Goal: The goal is to establish maternal immunization as an effective means for providing protection to the very young.

Accomplishments: We have successfully demonstrated in the mouse and pig model that maternal immunization is an effective way to protect the very young against pertussis. We are currently recruiting volunteers (pregnant mothers) for a clinical trial coordinated by Dr. S. Halperin, IWK Centre, Halifax.

Impact: If successful in humans too, this could have tremendous impact on children in both developing, as well as developed, countries.

Publications:

Elahi S, Buchanan RM, Babiuk LA and Gerdts V. 2006. Maternal immunity provides protection against pertussis in newborn piglets. *Infect Immun.* 74:2619-2627.

Fetal and neonatal immunization with DNA vaccines to understand development of the mucosal immune system

Need: The neonatal period is the time of greatest vulnerability to infectious disease either through vertical disease transmission (HIV, HCV, HBV) or horizontal transmission. Traditional concepts, developed from murine models, have suggested that the neonate may not be an appropriate target for vaccination but studies in many other animal models indicate that both systemic and mucosal immunization may be efficacious in the neonate.

Goal: Analyze development of the mucosal immune system and identify effective vaccine strategies to induce protective mucosal immune responses in the neonate.

Accomplishments: We have demonstrated that the mucosal immune system is functional *in utero* and that DNA vaccines targetting mucosal surfaces induce protective immune responses. Furthermore, there was no evidence that DNA vaccines induced immune tolerance even when delivered during the second trimester of gestation.

Impact: These observations provide strong evidence that the neonatal mucosal immune system is functional if appropriate vaccine delivery systems are used.

Publications:

Gerdtz V, Babiuk LA., van Drunen Little-van den Hurk S and Griebel PJ. 2000. Fetal immunization by a DNA vaccine delivered orally into the amniotic fluid. *Nature Medicine* 6:929-932.

Tsang CH, Mirakhur KK, Babiuk LA and Griebel PJ. 2007. Oral DNA Immunization in the Second Trimester Fetal Lamb and Secondary Immune Responses in the Neonate. *Vaccine* 25:8469-8479.

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National Institute
of Child Health &
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Biobehavioural responses during immunization in preterm infants

Need: Prolonged repetitive pain exposure during neonatal intensive care of infants born very preterm (gestational age \leq 32 weeks) leads to autonomic, hormonal and behavioural changes in the short term, and may alter pain reactivity in the long term. Animal studies suggest that neonatal pain exposure in immature organisms can induce changes in pain systems that may persist into adulthood. In human preterm infants, pain reactivity is altered in the neonatal intensive care unit, however, there has been little attention as to whether this persists after hospital discharge. Furthermore, mothers of extremely low gestational age infants are often under stress, due to concerns about their infant. Maternal behaviours are viewed as “hidden regulators” which may mediate pain expression in infancy, and may differ with varying “risk status” of the infant.

Goal: To compare pain responses (autonomic, hormonal, behavioural) in preterm versus term born infants at 4 months “corrected” age, and to examine concurrent effects of maternal stress, maternal behaviours, infant temperament and sex.

Accomplishments: We identified differences in biobehavioural reactivity and recovery to pain of immunization injections in preterm infants, as well as maternal behaviours that moderate pain expression.

Impact: This work contributes to understanding pain reactivity in preterm infants, and adds to development of simple effective parent interventions to distract infants during injections to reduce pain experience.

Publications:

Grunau RE, Weinberg J, Whitfield MF, Oberlander T and Tu MT. 2008. Does cortisol stress reactivity differ in preterm compared to full-term infants at 4 months corrected age? Poster, Society for Pediatric Research, Honolulu, May 2008.

Tu MT, Grunau RE, Whitfield MF and Weinberg J. 2007. Maternal behaviours mediate the cortisol response to immunization in preterm infants. Poster, Society for Research in Child Development, Boston, March 2007.

Cost and effectiveness of primary and influenza vaccination programs in Quebec

Need: Funding for vaccination programs should be dependent on the actual cost of their implementation. The actual cost, however, is unknown. Further, it is not known whether vaccinations provided in public clinics are more cost-effective for society than vaccinations in private clinics.

Goal: Determine the costs and effectiveness of vaccination programs for 0-2 year olds and influenza programs in Quebec.

Accomplishments: Vaccinating 0-2 year olds is more costly for society in public clinics, whereas influenza vaccinations in private clinics are more costly for society.

Impact: The results should provide the impetus for adjusting the funding of vaccination programs and reviewing the organization of first-line vaccination services.

Publications:

Guay M, Blackburn M, Clément P, Tremblay A, St-Hilaire C, Clouâtre AM, Rousseau L, Landry M, Pelletier A, Dionne M and St-Amand D. 2006. Coûts et efficacité du programme de vaccination des enfants de 0-2 ans au Québec. *Can J Infect Dis & Med Microb.* 17:377.

Guay M, Blackburn M, Pelletier A, Tremblay A, St-Hilaire C, Clouâtre AM, Rousseau L, Landry M, Clément P, Dionne M and St-Amand. 2006. Coûts et efficacité du programme de vaccination contre l'influenza au Québec. *Can J Infect Dis & Med Microb.* 17:359.

Guay M, Blackburn M, Pelletier A, Tremblay A, St-Hilaire C, Clément P, Clouâtre AM and Rousseau L. 2007. Étude sur les coûts et l'efficacité du programme de vaccination contre l'influenza au Québec - Institut national de santé publique du Québec, 151 pages.

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and Social Services (MSSS)

Maryse Guay
continued

Supported by:

MSSS, FRSQ et Programme de subventions en santé publique.

Guay M, Blackburn M, Clément P, Tremblay A, St-Hilaire C, Clouâtre AM, Rousseau L and Pelletier A. 2006. Étude sur les coûts et l'efficacité du programme de vaccination des enfants de 0-2 ans au Québec, Institut national de santé publique du Québec, 183 pages.

Barriers to vaccination and organization of vaccination services in Quebec

Need: The capacity of vaccination programs to provide the desired outcomes in regard to vaccine coverage is dependent on many factors. Barriers exist to the implementation of programs, and the vaccine coverage that is achieved is not always known. With a better understanding of barriers and vaccine coverage, the delivery of vaccination services could be adapted.

Accomplishments: Our research has provided a better understanding of the barriers that exist to vaccination and described both the organization of vaccination services and vaccine coverage results.

Impact: In light of the results obtained through our research, the barriers are the demand for vaccination (e.g. misinformation, false beliefs), the offering (e.g. reluctance about receiving the vaccination) and accessibility (e.g. vaccination services poorly suited to needs). Various adjustments to the organization of vaccination services must be made and greater emphasis must be placed on promoting vaccination with the public than with vaccinators themselves.

Publications:

Rousseau L, Guay M, Archambault D, Abdelaziz N and El'Mmala Z. 2007. Existe-t-il des barrières organisationnelles à l'accessibilité à la vaccination contre l'influenza et le pneumocoque. *Revue canadienne de santé publique* 98:105-110.

St-Amour M, Guay M, Clément P, Perron L, Baron G and Petit G. 2006. Are information leaflets useful for vaccinators and parents? *Vaccine* 24:2491-2496.

Maryse Guay
continued

Guay M, Gallagher F, Petit G, Menard S, Boyer G. Pourquoi les couvertures vaccinales chez les nourrissons de l'Estrie sont-elles sous-optimales, in press.

Guay M and Côté L. 2006. Enquête québécoise sur les couvertures vaccinales contre l'influenza et le pneumocoque 2005-2006. Rapport conjoint de l'Institut de la statistique du Québec et de l'Institut national de santé publique du Québec, Québec, 46 p.

Guay M, Dubé G, Côté L, Valiquette L, Boulianne N, Douville-Fradet M, Landry M, and Paré L. 2004. Enquête québécoise sur les couvertures vaccinales contre l'influenza et le pneumocoque 2003-2004, Rapport conjoint de l'Institut de la statistique du Québec et de l'Institut national de santé publique du Québec, Montréal, 37 p.

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Exploration of key factors influencing acceptance of influenza immunization among pregnant women

Need: As Canadian Provinces and Territories consider implementation of influenza immunization programs that include all pregnant women as recommended by the National Advisory Committee on Immunization (NACI), it is essential to have a clear understanding of pregnant women's perspectives on influenza vaccination during pregnancy to inform program planning and optimize program impact.

Goal: The goal of this project was to explore the key determinants of Canadian women's willingness to accept influenza immunization during pregnancy in order to inform implementation of a universal vaccination program in this population.

Accomplishments/Outcomes: Health care provider recommendations emerged as a key factor contributing to acceptance of influenza vaccine by pregnant women. However, despite 61% of women stating that they would receive the influenza vaccine while pregnant if their doctor recommended it, only 20% said their doctor had discussed influenza vaccination during their pregnancy.

Impact: These data highlight the need for imaginative, effective and evaluable public and professional education campaigns if implementation of a universal influenza vaccination program in this population is to be effective.

Immunization with acellular pertussis vaccine during pregnancy and post-partum: safety, immunogenicity and kinetics

Need: Pertussis during the first months of life is associated with high rates of morbidity; virtually all of the deaths from pertussis in Canada occur in the first two months of life, before the immunization series can be initiated. If post-partum immunization of women can provide sufficient rapid protection of the mother, this might prevent introduction of infection to the susceptible newborn (“cocoon strategy”). Immunization during pregnancy could provide passive antibody which might protect the infant in the interval before initiation of the infant’s own immunization series.

Accomplishments: In two pilot studies, we demonstrated that a single dose of acellular pertussis vaccine combined with diphtheria and tetanus toxoids (Tdap) in women of child-bearing age (pilot 1) and post partum women (pilot 2) induces a rapid rise in antibodies against all pertussis antigens (pertussis toxoid, filamentous hemagglutinin, pertactin, fimbriae 2/3). Rises in serum IgG and IgA antibodies against all antigens were detectable by 5 to 7 days, reaching peak levels by 10-14 days post-immunization. Although suggestive of an anamnestic response, the protection of the mothers still would leave the infant at risk for 1-2 weeks.

Impact: The results of the pilot studies provided support for initiation of a randomized clinical trial of Tdap vs Td administered to women during the mid 3rd trimester. Antibody levels in the mothers (blood, breast milk) and the infants at birth and before and after each of their primary and booster doses will determine whether passive antibody can be provided to newborns by immunizing their mothers during pregnancy and whether this antibody will interfere with the infants own response to their primary vaccination series. This clinical trial is currently enrolling.

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Supported by:
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sanofi pasteur.

Scott A Halperin
and
Beth Halperin
continued

Publications:

Halperin BA, McNeil S, Langley JM, Mutch J, MacKinnon-Cameron D and Halperin SA. 2006. Kinetics of the serum IgG and IgA antibody response in healthy women of child-bearing age after immunization with Tdap. *Can J Infect Dis Med Microbiol.* 17:354 Abstract O20.

Halperin BA, McNeil S, Langley JM, Mutch J, MacKinnon-Cameron D, Allen V and Halperin SA. 2008. Kinetics of the IgG and IgA antibody response in post-partum women after immunization with adult formulation diphtheria and tetanus toxoids and acellular pertussis vaccine (Tdap). Presented at the 11th Annual Conference on Vaccine Research, Baltimore, MD Poster P35.

Mechanism of female sex hormones actions on immune responses to HSV-2 infection

Need: Mucosal surfaces of the body are the site for initiation of the majority of infections. These surfaces also have unique microenvironments. In the genital mucosa, female sex hormones are known to influence susceptibility to sexually transmitted infections. They are also known to modulate immune responses in the genital tract. Efforts to develop effective STI vaccines have to induce and sustain immune responses in the genital mucosa where these hormones have a powerful influence. Therefore, it is very important to understand how female sex hormones influence immune responses to sexually transmitted infections. We are focussing on sexually transmitted viruses, HSV-2 as a model system that can be applied to other bacterial and viral pathogens.

Goal: The goal of this research project has been to

- (1) determine the role played by female sex hormones in modulating susceptibility to HSV-2 in the genital tract,
- (2) determine role of sex hormones in regulating initiation and resolution of mucosal immune responses to HSV-2 and
- (3) determine the influence of sex hormones on initiation of immune responses beyond genital tract.

Accomplishments: We were able to show clearly using a mouse model of genital HSV-2 infection that (1) estradiol regulated the susceptibility to HSV-2, while progesterone mainly induced inflammation following viral infection, (2) following immunization with attenuated virus under the influence of different hormones, the outcomes were very different, (3) immune responses to HSV-2 were influenced by the local hormonal environment. Hormones influence both the quality of immune responses initiated as well as the disease pathology, and (4) similar to effects seen during local immunization, systemic immunization (subcutaneous and intranasal) with attenuated HSV-2 was also influenced by sex hormones.

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Supported by:
CIHR

Impact: These results and ongoing studies have important implications in the following areas: (1) it highlights the importance of understanding susceptibility and immune responses in women during the menstrual cycle, following hormonal contraceptive use and hormone replacement therapy, (2) it highlights the importance of taking hormonal environment into consideration for designing of effective mucosal vaccine for STIs, (3) it supports the argument that vaccine strategies in the 21st century have to be far more advanced than current approaches, in particular gender-specific mucosal vaccine strategies need to be considered seriously!

Publications:

Kaushic C, Ashkar AA, Reid L and Rosenthal K. 2003. Progesterone increases susceptibility and decreases immune responses to genital herpes infection. *J Virol.* 77:4558-4565.

Gillgrass A, Ashkar A, Rosenthal K and Kaushic C. 2003. Prolonged exposure to progesterone prevents induction of protective mucosal responses following intravaginal immunization with attenuated herpes simplex virus, type 2. *J Virol.* 77:9845-9851.

Gillgrass A, Fernandez S, Rosenthal K and Kaushic C. 2005. Estradiol regulates susceptibility following primary exposure to genital herpes simplex virus type 2, while progesterone induces inflammation. *J Virol.* 79:3107-3116.

Gillgrass A, Tang V, Towarnicki K, Rosenthal K and Kaushic C. 2005. Protection against genital herpes infection in mice immunized under different hormonal conditions correlates with induction of vaginal-associated lymphoid tissue (VALT). *J Virol.* 79:3117-3126.

Bhavanam S, Gillgrass A and Kaushic C. Systemic immunization under the effect of estradiol leads to better protection against genital HSV-2 challenge compared to progesterone communicated.

Epidemiology of HPV-related diseases and associated health-care resource utilization and costs in Manitoba

Need: Very little is known about the burden of HPV-related disease in Canada.

Goal: The study has three components: 1) Descriptive epidemiology of ano-genital warts. 2) Descriptive epidemiology of cervical dysplasia, *in situ* and invasive cervical cancer. 3) Utilization of health services and costs associated with the diagnosis and treatment of ano-genital warts and cervical abnormalities.

Accomplishments: The first report on the epidemiology of ano-genital warts in Manitoba has been completed. The report shows the trends in incidence, prevalence and lifetime risk over a 20 year period (1985-2004). The reports on cervical abnormalities and on resource utilization and costs are in progress.

Impact: The study provides baseline data that can be used to assess the impact of HPV vaccines.

Uptake of Gardasil in Manitoba prior to a provincial vaccination program

Need: To our knowledge there is no other study underway in Canada examining the uptake of the HPV vaccine(s).

Goal: The aims of the study are to develop a method of identifying people vaccinated against HPV using prescription and physician records and to determine if there are disparities in the uptake of the HPV vaccine.

Accomplishments: The study has just received all the required approvals (e.g. ethics) and the data extracts are in progress.

Impact: The study will lay the groundwork for a HPV vaccine registry. The registry will form the basis of an extensive HPV vaccine surveillance program in Manitoba.

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Supported by:
Merck Frosst Canada

Supported by:
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Chemical, Biological,
Radiological and Nuclear
Research and Technology
Initiative (CBRNE).

Mucosal delivery of adenovirus-based vaccine protects against ebola virus even in the presence of pre-existing immunity

Need: We have generated a new adenovirus-based vaccine that can also protect in the presence of pre-existing immunity. This vaccine is currently being evaluated in nonhuman primates against Ebola virus. It will need to be evaluated in Phase I clinical trials in 2 years. Setting up Phase I trials is really challenging in Canada.

Goal: The research team has contacted several clinicians/scientists with access to a clinical environment suitable for a Phase I trial. The trial should be prepared and submitted for funding.

Accomplishments: see above

Impact: Providing (first responders) with a clinical formulation of an effective Ebola vaccine.

Publications:

Patel A, Zhang Y, Croyle M, Tran K, Gray M, Strong J, Feldmann H, Wilson JM and Kobinger GP. 2007. Mucosal Delivery of Adenovirus-Based Vaccine Protects Against Ebola Virus Infection in Mice. *Journal of Infectious Diseases* 196 Suppl 2:S413-20.

Croyle M, Patel A, Zhang Y, Tran K, Gray M, Strong J, Feldmann H and Kobinger GP. 2008. Nasal Delivery of Adenovirus-Based Vaccine Bypasses Pre-existing Immunity to the Vaccine Vector submitted.

Vaccine development and evaluation for protection against avian influenza virus

Gary Kobinger
continued

Need: Several vaccines including VLPs-, adenovirus-, DNA-based as well as the conventional inactivated vaccine were generated and tested in animal models of influenza infection. Personnel is needed for accelerating the evaluation of the vaccines in larger animal models, submitting recommendations to Canadian decision makers including PHAC and for the development of a clinical grade vaccine that can protect against several strains of avian influenza virus.

Supported by:
CIHR, PHAC

Goal: Identify the best performing vaccine strategy against H5N1 and also the most likely to be quickly deployed in the event of a sudden outbreak.

Accomplishments: We have identified the most efficient vaccine platform and the best antigenic combination to protect against heterologous strains of avian influenza. These need to be combined, tested *in vivo* and compared to the conventional inactivated vaccine.

Impact: Critical recommendations to Canadian decision makers to make a optimized assessment supported by scientific observations concerning influenza outbreak management.

Publications:

Laddy DJ, Yan J, Corbitt N, Kobasa D, Kobinger GP and Weiner DB. 2007. Immunogenicity of novel consensus-based DNA vaccines against avian influenza. *Vaccine* 25:2984-2989.

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Supported by:

Burroughs Wellcome Career Award in the Biomedical Sciences (100%)

Supported by:

NIH RO1 (80%); CCHCSP (10%), Burroughs Wellcome Career Award in the Biomedical Sciences (10%).

Neonatal vaccines

Need: Most vaccine-preventable disease morbidity and mortality strikes the very young (e.g. pertussis), yet most vaccine induced protection is only provided later in life.

Accomplishments: Identified new approach to neonatal vaccination.

Impact: Allows dissection of essential parameters in the neonatal immune response.

Publications:

Kollmann TR, Reikie B, Blimkie D, Way SS, Arispe K, Shaulov A, Hajjar AM and Wilson CB. 2007. Induction of protective immunity to *Listeria monocytogenes* in neonates. *J Immunol.* 178:3695.

High-throughput vaccine adjuvant screening

Need: Novel adjuvants need to be efficiently and rapidly screened for potential activity.

Accomplishments: Designed and optimized rapid high-throughput innate immune modulator screen that works with a minimal blood volume.

Impact: Optimized standard operating procedures to allow scientists in academia and industry to rapidly screen for novel adjuvants. This platform also allows rapid innate immune deficiency screening.

Publications:

Jansen K, Blimkie D, Furlong J, Hajjar AM, Rein-Weston A, Crabtree J, Reikie B, Wilson CB and Kollmann TR. 2008. Polychromatic flow cytometric high-throughput assay to analyze the innate immune response to Toll-like receptor stimulation. *J Immunol Methods*, in press.

Ontogeny of innate immune reactivity

Need: While most vaccines are given in early life, little is known about the development of the innate immune system in the first few years of life.

Accomplishments: Set up a large cohort of subjects to be followed from birth up to pre-school age to screen for innate immune reactivity and assess the impact on vaccine outcome.

Impact: Identification of optimal vaccine adjuvants for early life.

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continued

Supported by:

NIH RO1, CCHCSP, Burroughs Wellcome Career Award in the Biomedical Sciences.

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CIHR

Photodynamic therapy-generated cancer vaccine

Need: More effective immunotherapy of various types of cancerous lesions is needed.

Goal: Photooxidative changes induced in tumour cells by photodynamic therapy render them more immunogenic, and the goal was to exploit this for therapeutic benefit.

Accomplishments: Using mouse tumour models, we showed that photodynamic therapy-generated autologous whole-cell cancer vaccines can eradicate established tumours.

Impact: Having determined major elements of the mechanisms underlying anti-tumour immune effect of these vaccines, we are now in position to identify modifications that would further improve their therapeutic impact.

Publications:

Korbelik M, Stott B and Sun J. 2007. Photodynamic therapy-generated vaccines: relevance of tumour cell death expression. Br J Cancer 97:1381-1387.

Evaluation of Ontario's universal influenza immunization program (UIIP)

Need: Annual epidemics of influenza continue to cause worldwide morbidity, mortality and societal disruption. When there is good match to circulating strains, influenza vaccines are generally efficacious and cost-effective for most age groups. In October 2000, Ontario initiated the world's first large-scale universal influenza immunization program (UIIP) to provide free influenza vaccinations for the entire population 6 months of age or older.

Goal: We evaluated the effect of Ontario's UIIP on influenza vaccination rates, hospitalizations, deaths, visits to emergency departments and physician offices and antibiotic prescriptions.

Accomplishments: We found that introduction of Ontario's UIIP was associated with greater increases in influenza vaccination rates compared to other provinces for younger age groups who were not previously covered by conventional targeted immunization programs. We also found relative decreases in influenza-associated mortality, health-care use (hospitalizations and visits to emergency departments and physician offices) and antibiotic prescriptions in Ontario compared with other provinces.

Impact: The results of these studies will assist policy-makers in deciding whether or not to implement universal influenza immunization programs in their respective jurisdictions.

Publications:

Kwong JC, Rosella L and Johansen H. 2007. Trends in influenza vaccination in Canada, 1996-2005. Health Reports (Statistics Canada, Catalogue 82-003) 18:1-11.

Kwong JC, Sambell C, Johansen H, Stukel TA and Manuel DG. 2006. The effect of universal influenza immunization on vaccination rates in Ontario. Health Reports (Statistics Canada, Catalogue 82-003) 17:31-40.

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Supported by:

PHAC (80%), CIHR
(20%)

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Supported by:
CIHR (100%)

***In vivo* inducible T cell receptor expression to study T cell activation, differentiation and survival**

Need: Despite a very good understanding on how T lymphocytes recognize foreign antigens such as infectious agents, we still do not understand the molecular program and the signals that are required for the generation and long-term maintenance of memory T cells. The generation of a long-lived pool of memory T cells is the goal to achieve for successful vaccination.

Goal: The objective of this proposal is to determine which signals influence the generation and maintenance of memory T cells.

Accomplishments: Our work showed that IL-7 receptor expression is not always a good marker to identify the precursors of memory T cells among effectors and that selective expression of IL-7 receptor should not be used to predict the success of vaccination.

Impact: This tells us that we need to develop other markers to predict the success of vaccination.

Publications:

Lacombe M-H, Hardy M-P, Rooney J and Labrecque N. 2005. Interleukin-7 receptor expression levels do not identify CD8⁺ memory T lymphocyte precursors following peptide immunization. *J Immunol.* 175:4400-4407.

Regulation of hematopoiesis and memory T cell generation by IL-21

Need: To improve the success of vaccination, we need to identify the factors that are involved in the generation and maintenance of memory T lymphocytes.

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Goal: The goal of the project was to overexpress IL-21 *in vivo* to evaluate its possible role in the generation and maintenance of memory T cells.

Accomplishments: We have shown that IL-21 is a very good survival factor for memory T cells and that its overproduction leads to the accumulation of memory T cells.

Impact: The impact of our work is that IL-21 inclusion into vaccines could be useful to increase the generation of memory T cells. Furthermore, the promotion of memory T cell survival by IL-21 could eventually be used to help us to study memory T cells *in vitro* and to maintain memory T cells in the elderly.

Publications:

Ostiguy V, Allard E-L, Marquis M, Leignadier J and Labrecque N. 2007. IL-21 promotes T lymphocyte survival by activating the phosphatidylinositol-3-kinase signalling cascade. *J Leukoc Biol.* 82:645-656.

Allard E-L, Hardy, M-P, Leignadier J, Marquis M, Rooney J, Lehoux D and Labrecque N. 2007. Overexpression of interleukin-21 promotes massive CD8⁺ memory T cell accumulation. *Eur J Immunol.* 37:3069-3077.

T cell survival and differentiation: role of the T cell receptor and impact on lymph node homeostasis

Need: A better understanding of the role of TCR (receptor that recognize infectious agent) signal strength in the generation and maintenance of immune memory will bring valuable information for the development of improved strategies to ameliorate vaccination.

Goal: The objectives of this proposal are: 1) to understand how the strength of TCR signaling influences the differentiation of effector CD8⁺ T lymphocytes into memory

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T cells and 2) to evaluate how TCR-mediated T cell survival regulates memory T cell homeostasis.

Accomplishments: 1) We have shown that TCR signals are not necessary for the long-term survival of memory T cells. Moreover, we have shown that T cells produce or express a factor that is necessary for the maintenance of the different cell types that are found in secondary lymphoid organs (site of the induction of the immune response) 2) We have shown that the amount of antigen that is used in immunization influences the generation of memory T cells but not the generation of effectors.

Impact: These results will help us to design better a vaccination strategy in immunodeficient patients. In addition, our results illustrate the importance of carefully titrating the amount of antigen that is used for vaccination. Furthermore, our results also show that we should not only look at the generation of effector T cells to predict the success of vaccination.

Towards the identification of the serological correlate of protection against pneumococcal disease: a high throughput opsonophagocytosis assay for 13 serotypes

Need: The licensure and marketing of a 7-valent pneumococcal conjugate vaccine made clinical efficacy trials with new vaccines ethically dubious and statistically impossible. Therefore, to license a new pneumococcal conjugate vaccine, it was deemed sufficient to show serologic non-inferiority compared to a licensed vaccine. This approach requires that the serological data is correlated with protection, which has not been demonstrated using ELISA antibody concentrations.

The research team was to develop and validate an opsonophagocytosis method in cooperation with other labs, including CDC, CBER and WHO reference laboratories. The goal was to have an assay which generated statistically similar results in different locations. Our local goal was to have the ability to test large numbers of samples with different serotypes over a short period of time.

Accomplishments: A high throughput method was developed using innovations including an automated plate reader and computerized analysis. This assay was shown to correlate within defined limits with 5 different laboratories, but with much greater throughput. Subsequent research using this assay has shown that it correlates with protective efficacy against pneumococcal otitis media better than ELISA antibody concentrations.

Impact: This high throughput assay was used to generate serological non-inferiority data in a Phase III efficacy trial for the licensure of a new pneumococcal conjugate vaccine.

Publications:

Laferrière C, Wauters D, Poolman J, Nurrku A and Kayhty H. 2002. Estimation of the Antibody Concentration at Threshold

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continued

Opsonophagocidal Activity: Is Serotype 19F Different? Third International Symposium on Pneumococci and Pneumococcal Diseases, Anchorage, Alaska.

Romero-Steiner S, Frasch C, Concepcion N, Goldblatt D, Kayhty H, Vakevainen M, Laferrière C, Wauters D, Nahm MH, Schinsky MF, Plikaytis BD and Carlone GM. 2003. Multilaboratory evaluation of a viability assay for measurement of opsonophagocytic antibodies specific to the capsular polysaccharides of *Streptococcus pneumoniae*. Clin Diagn Lab Immunol.10:1019-1024.

Schuerman L, Prymula R, Henckaerts I and Poolman J. 2007. ELISA IgG concentrations and opsonophagocytic activity following pneumococcal protein D conjugate vaccination and relationship to efficacy against acute otitis media. Vaccine 25:1962-1968.

A Canadian model for estimating influenza-attributed illness

Need: Although annual influenza viral epidemics are recognized as an important cause of morbidity and mortality, the burden of illness has not been well quantified in the Canadian population. We sought to develop a Canadian model for estimating influenza-attributed illness based on techniques used in other countries, and using existing health utilization databases and the national respiratory virus surveillance system. The team consists of members from public health, university and health-care communities.

Impact: A model has been developed which demonstrates a good fit with virus activity. This data has been used to inform vaccine policy and identify future potential improvements needed in health databases and surveillance systems.

Publications:

Schanzer DL, Tam TW, Langley JM and Winchester BT. 2007. Influenza-attributable deaths, Canada 1990-1999. *Epidemiol Infect.* 135:1109-1116.

Schanzer DL, Langley JM and Tam TWS. 2007. Influenza-attributed hospitalization rates among pregnant women in Canada 1994-2000. *J Obstet Gynaecol Can.* 29:622-629.

Schanzer DL, Langley JM and Tam TWS. 2006. Hospitalizations attributable to influenza and other viral respiratory illnesses in Canadian children. *Pediatr Inf Dis J.* 25:795-800.

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concertas pour la santé,
CIHR Pandemic
Preparedness Strategic
Research Priority

Characterization and improvement of the intrinsic adjuvant properties of papaya mosaic virus-like particles: An innovative vaccine platform

Need: Although vaccines have played an important role in preventing infectious disease, the technology that is used in commercial vaccines is aging and inefficient since several vaccines on the market only provide a partial protection to pathogens. A new adjuvant and vaccine platform is needed that will permit the development of innovative vaccines that will trigger both humoral and the cellular responses of the immune system in order to improve protection. The threat of pandemics renders the development of new technologies a priority for protection of humans to newly emerging diseases.

Goal: The goal of the project is to characterize the recognition of a new plant virus-based adjuvant by the innate immune system and develop an improved version of this adjuvant using protein engineering to increase its immunogenicity and the formation of the complex with the antigen.

Accomplishments: We proved that the plant-based vaccine platform could trigger both arms of the immune system: the humoral and the cellular response simultaneously. We showed that the platform could induce cross-presentation of CTL epitope very efficiently at the surface of dendritic cells. We made two proofs of concept and obtained 100% protection in a typhoid fever model to 500 lethal dose (LD50) and 100% protection to 4 lethal dose (4LD50) of an influenza virus. We are currently aiming to bring the adjuvant into Phase I trials in humans and use this technology for improvement of commercial vaccines.

Impact: We believe the platform will allow the improvement of existing vaccines by increasing the humoral and the CTL response to conserved epitopes of the pathogen. For example, it is anticipated that modifying a commercial flu vaccine with the platform will make the vaccine universal to any strain of influenza, including the

avian flu. Furthermore, we believe the immunogenic properties of this platform will allow the development of vaccines to chronic diseases like hepatitis C virus, HIV-1 infection and several forms of cancer that need the induction of a strong CTL response.

Publications:

Acosta-Ramirez E, Perez-Flores R, Majeau N, Pastelin-Palacios R, Gil-Cruz C, Ramirez-Salda M, Manjarrez-Orduo N, Cervantes-Barragan L, Santos-Argumedo L., Flores-Romo L, Becker I, Isibasi A, Leclerc D and Lopez-Macias C. 2007. Translate innate response into long-lasting antibody response by the intrinsic antigen-adjuvant properties of papaya mosaic virus. *Immunology*, in press.

Lacasse P, Denis J, Lapointe R, Leclerc D and Alain Lamarre. 2007. Novel plant virus-based vaccine induces protective CTL-mediated antiviral immunity through dendritic cell maturation. *J Virol.*, in press.

Denis J, Majeau N, Acosta-Ramirez E, Savard C, Bedard M.-C, Simard S, Lecours K, Bolduc M, Para C, Willems B, Shoukry N, Tessier P, Lacasse P, Lamarre A, Lapointe R, Lopez-Macias C and Leclerc D. 2007. Immunogenicity of Papaya Mosaic Virus like particles fused to a hepatitis C virus epitope: evidence for the critical function of multimerization. *Virology* 363:59-68.

Leclerc D, Beauseigle D, Denis J, Morin H, Pare C, Lamarre A and Lapointe R. 2007. Proteasome-independent MHC class I cross-presentation mediated by papaya mosaic virus-like particles leads to the expansion of specific human T cells. *J Virol.* 81:1319-26.

Development of an innovative treatment to lung cancer

Need: Although some success is being achieved in the treatment of cancer, most authorities agree that we could in most cases improve the condition rather than cure it. More success has also been achieved in some types of cancer than in others, and early diagnosis has been responsible, at least in part, for the improved aetiology. Being able to tackle the tumour before it spreads to the lymph

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nodes or other tissues greatly enhances success rates but, in the case of non-small cell lung cancer, progress has been slow. Surgical removal is still regarded as the most effective treatment although 5-year survival for non-small cell lung cancer (NSCLC) is still only at 13-14%. Surgery is of limited value after Stage II, where reliance on radiotherapy and cytotoxic chemotherapy is prevalent. There is a high correlation (80-85%) between patients that develop lung cancer and the practice of smoking. Despite this, the number of smokers is still predicted to increase globally alongside the growth in world population. The fast growth of the economies of several Asiatic countries also encourages the consumption of tobacco. WHO estimates that 47.5% of men and 10.3% of women are smokers. Smokers may also affect the health of people surrounding them, especially children that share the same living space. The incidence of lung cancer is consequently progressing at a similar rate. Lung cancer is the most devastating form of cancer and accounts for 13% of all cancers and 30% of all cancer deaths in the USA. There is currently no cure for the disease and the only therapies available are based on the use of dangerous toxins or radiotherapy. There is clearly a high level of unmet clinical need.

Goal: One of the major difficulties encountered in immunotherapy of cancer is to trigger a cytotoxic response to self-antigen. Although important proofs of principle have been established in tumour immunotherapies, major improvements are needed to enhance the efficacy of tumour vaccines. It was recently shown that repetitive and crystalline structures, like PAL, are able to overcome tolerance and can efficiently induce an immune response to self-antigen. We previously showed that a plant virus-based platform can trigger an immune response to insulin, an abundant self-antigen produced in the pancreas and in both arms of the immune system: the humoral and the cytotoxic response. Therefore, the association of the self-antigen DKK1 to the platform will generate a new candidate vaccine, which will trigger an autoimmune response to DKK1. The treatment of lung cancer patients with this vaccine will result in the development of antibodies specific to DKK1 and a cytotoxic response to cancer cells expressing DKK1. This project will be very

useful to validate this concept with respect to lung cancer. Furthermore, because DKK1 is also found in other cancers, the same vaccine could also be used for treatments in other cancers.

Accomplishments: To date, we have generated constructs that combine DKK-1 antigen to the vaccine platform. The protein engineering was very successful. We are now testing the constructs *in vitro* in human cells to trigger proliferation of CD8⁺ DKK-1-specific T cells.

Impact: We anticipate to be able to develop a new treatment in immunotherapy to lung cancer using this approach. Considering that there is currently no efficient treatment for this cancer, we believe that the development of this technology is crucial for Canadians. Furthermore, since DKK-1 is a good target for several forms of cancer including kidney cancer, melanomas and breast cancer, it is exciting to believe that the same molecules could be used to treat several cancers.

Development of a universal influenza A candidate vaccine

Need: Existing vaccines contain three killed or attenuated virus strains: one A (H3N2) virus, one A (H1N1) virus and one B virus. The viruses in the vaccine change each year based on international surveillance and scientists' estimations about which types and strains of viruses will circulate in a given year. During the 20th century, the emergence of several new influenza A virus subtypes caused three pandemics: "Spanish flu," [A (H1N1)] (1918), "Asian flu" [A (H2N2)] (1957) and the "Hong Kong flu" [A (H3N2)] (1968) all of which spread around the world within a year of being detected. Experts believe, according to the existing vaccine paradigm, that vaccination would not be effective for preventing a pandemic, because they target individual viral strains and not the entire influenza virus class. Considering the importance of the genetic drift and exchanges between circulating influenza viruses, vaccination with inactivated viruses would be limited. There is, therefore, an urgent and unmet need for the development of a

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Initiative

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universal influenza A vaccine through induction of a CTL response toward influenza conserved epitopes.

Goal: Development of a universal influenza A candidate vaccine. The candidate vaccine will contain two components, PapMV-VLPs-M2e and a complex made of a high avidity PapMV-VLPs and M1 or NP. In parallel, we will develop several versions of the adjuvant to improve the immunogenicity of the commercial flu vaccine to improve protection capacity.

Accomplishments: A manuscript was submitted this week on a vaccine candidate based on the use of the M2e peptide from which we obtained 100% protection to a challenge of 4LD50 of influenza.

Impact: Our second step is to engineer the platform to trigger efficiently a CTL response to the conserved viral proteins NP and M1.

Publications:

Denis J, Zhao Y, Acosta-Ramirez E, Patry R-M, Hamelin M-E, Koukavica I, Baz M, Abed Y, Lecours K, Savard S, Pare C, Lopez Macias C, Boivin G and Leclerc D. 2008. Development of a Universal Influenza A vaccine based on the M2e peptide fused to the Papaya Mosaic Virus (PapMV) vaccine platform. Vaccine, submitted.

Use of commensal *Streptococcus gordonii* as a live oral vaccine vehicle.

Need: Needle-free mucosal vaccines are needed.

Accomplishments: We demonstrated that *S. gordonii* can be genetically engineered to express candidate vaccine antigens and the recombinant *S. gordonii* can induce an immune response during oral colonization in mice. Further work has focussed on understanding how the immune cells respond to *S. gordonii*. Additionally, the most recent work showed that antigen-targeting using single chain variable fragment antibody is a promising approach to induced an enhanced immune response to antigen produced by *S. gordonii*.

Impact: The approach, if successful, will provide an innovative, “cheap” and effective means to protect infectious diseases. The approach has the potential to achieve immunity at population level by virtue of the fact that *S. gordonii* is ubiquitously present among humans.

Publications:

Knight JB, Halperin SA, West KA and Lee SF. 2008. Expression of a functional single chain variable fragment antibody against the complement receptor 1 in *Streptococcus gordonii*. Clin Vaccine Immunol., in press (June issue).

Chan, KG, Mayer M, Davis EM, Halperin SA, Lin TJ and Lee SF. 2007. The roles of D-alanylation of *Streptococcus gordonii* lipoteichoic acid in innate and adaptive immunity. Infect Immun. 75:3033-3042.

Mallaley PP, Halperin SA, Morris A, MacMillian A and Lee SF. 2006. Expression of pertussis toxin S1 fragment by inducible promoters in oral streptococci and immune responses elicited during oral colonization in mice. Can J Microbiol. 52:436-444.

Lee CW, Lee SF and Halperin SA. 2004. Expression and immunogenicity of a recombinant diphtheria toxin fragment A in *Streptococcus gordonii*. Appl Environ Microbiol. 70:4569-4574.

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Immunotherapeutics
(CANVAC).

Vaccine development for hepatitis C

Need: Hepatitis C is a devastating liver disease worldwide. There are more than 170 million people infected by the hepatitis C virus. A Canadian hepatitis C model has estimated that the economic burden of hepatitis C will increase more than 50% in the next 40 years. There is no vaccine available. As such, the development of vaccines for hepatitis C becomes more and more urgent.

Goal: To evaluate a number of vaccination strategies to induce potent and effective immune responses against the hepatitis C virus.

Accomplishments: We have designed a novel HCV envelope protein-2 (E2) vaccine, namely the hypervariable region-1 was replaced by the signal peptide sequence of the tissue plasminogen activator and the hydrophobic region at the carboxyl-terminus was removed. Intradermal injection of the E2 DNA vaccine induced strong Th1-like immune responses in mice. In piglets, the E2 DNA vaccine elicited moderate and more balanced immune responses. A DNA vaccine prime and protein boost vaccination strategy induced significantly higher E2-specific antibody levels and shifted the immune response towards Th2-like in piglets.

Impact: The HCV E2 DNA vaccine developed in this study should be further tested in primate models with hepatitis C virus challenge to demonstrate protective activity of the vaccine.

Publications:

Li Y, Kang H-N, Babiuk LA and Liu Q. 2006. Elicitation of strong immune responses by a DNA vaccine expressing a secreted form of hepatitis C virus envelope protein E2 in murine and porcine animal models. *World Journal of Gastroenterology* 12:7126-7135.

Influenza in pregnancy

Need: NACI had asked for Canadian data on risk of influenza in pregnancy upon which to develop recommendations as previous large data had only come from American Tennessee Medicaid patients (i.e. inner city, low socioeconomic class etc).

Goal: A large cohort study of pregnant women using linked administrative databases to determine risk of hospitalization and/or physician visit for respiratory illness during flu season vs risk in flu season prior to pregnancy.

Accomplishments: This study demonstrated a significant increase in risk of serious illness with influenza in pregnant women especially in the third trimester and also especially in co-morbidity. Data was taken into account with change in NACI recommendations for use of influenza vaccine in 2007.

Impact: Change in vaccine recommendations.

Publications:

Dodds L, McNeil SA, Fell DB, Allen VM, Coombs A, Scott J and MacDonald N. 2007. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *CMAJ* 176:463-468.

McNeil SA, Dodds L, Allen VM, et al. 2007. Influenza vaccine programs and pregnancy: new Canadian evidence for immunization. *J Obstet Gynaecol Can.* 29:674-676.

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Describing the burden of illness of abnormal cervical pap smear test results and external ano-genital warts in Canada [PISCES: Psychosocial Impact of Abnormal Smear Pap and Condylomas in Canada: an Epidemiological Study]

Need: With the regulatory approval of the quadrivalent HPV vaccine in Canada, the ensuing NACI statement on its use and widespread adoption in clinical practice, there is an urgent need to quantify and qualify the psychosocial impact of HPV disease and its associated burden of illness. Determining the psychosocial impact of experiencing external genital warts and abnormal Pap test results is essential for assessing the clinical and economic value of different HPV vaccination strategies. However, there is a lack of data on this aspect of the burden of HPV infections. Notably, the health utility lost has not been evaluated. Health utility values are necessary to calculate the quality-adjusted-life-years (QALY) lost associated with a given health condition. QALYs are the gold-standard for evaluating the benefit of an intervention in cost-effectiveness analyses. As such, assessment of the psychosocial impact of HPV-related conditions and the health-care utilization associated with their management is required to understand the burden of HPV infections and essential for assessing cost effectiveness of HPV vaccination.

Goal: This is a Canadian, multicentre, clinic-based prospective cohort study designed with three main objectives: (i) To assess the psychosocial effect of abnormal Pap test results (ii) To assess the psychosocial effect of external ano-genital warts, and (iii) To determine the efficacy of HPV E6/E7 oncogene testing.

- (i) Impact of abnormal Pap test result:
 - a) To describe the psychosocial effect of Pap abnormalities.
 - b) To describe the Canadian health-care resource utilization associated with Pap abnormalities.
 - c) To assess the genotype-specific distribution of HPV infection in women aged 30 years and above with Pap abnormalities.

- (ii) Impact of external ano-genital wart:
 - a) To describe the psychosocial effect of external ano-genital warts in men and women.
 - b) To describe the Canadian health-care resource utilisation associated with external ano-genital warts.
- (iii) Efficacy of E6/E7 oncogene testing:
 - a) Determine the efficacy of HPV E6/E7 oncogene testing to identify women at increased risk for cervical cancer and its precursor lesions in comparison with HPV DNA screening, with histology as the gold standard.
 - b) Determine the application of E6/E7 mRNA testing in ASC triage, in comparison with HPV DNA testing, with histology as the gold standard.
 - c) Determine the efficacy of self collected cervicovaginal tampon samples for E6/E7 mRNA testing.

Accomplishments: The PISCES study has been able to provide data not presently available for characterizing the overall burden of HPV infections. This is the first study to measure health utilities in men and women with external genital warts in addition to the health utility lost by women receiving abnormal Pap test results.

Impact: These estimates of health utilities have been used to assess the QALY lost associated with HPV-related ano-genital warts and abnormal Pap tests and evaluate the cost-effectiveness of alternative HPV vaccination strategies. PISCES will be the first study to follow subjects up prospectively towards quantifying the health utilities lost associated with HPV-related diseases and provide a clinical picture of the related burden of illness.

Publications:

Sénécal M, Brisson M, Maunsell E, Franco EL, Ferenczy A, Ratnam S, Coutlée F, Palefsky JM and Mansi JA. 2006. Quality of Life Lost Associated with External Genital Warts: Preliminary Baseline Analyses from a Prospective Cohort

James A Mansi
continued

Study. 24th International papillomavirus conference, Beijing, China. November 3-9, 2006. (Poster)

Sénécal M, Maunsell E, Brisson M, Franco EL, Ferenczy A, Ratnam S, Coutlée F, Palefsky JM and Mansi JA. 2006. Psychosocial Effects of Receiving an Abnormal Pap result: Preliminary Analyses from a Prospective Cohort Study. 24rd International papillomavirus conference, Beijing, China. November 3-9, 2006. (Poster)

Sénécal M, Maunsell E, Ferenczy A, Franco EL, Ratnam S, Coutlée F, Palefsky JM, Foucart S, Brisson M and Mansi JA. 2006. Psychological impact of cervical screening and condylomas: an epidemiological study (PISCES) 23rd International papillomavirus conference, Prague, Czech Republic. September 1-7, 2006. (Poster)

Supported by:
Merck Frosst Canada Ltd.

Measuring herpes zoster and post-herpetic neuralgia associated burden of illness, health-care utilization and health-care costs in Canada: An epidemiological study [M.A.S.T.E.R.: Masuring & Assessing Shingles Through Education and Research]

Need: Patient suffering, loss of ability for self-care, financial implications of careers, and primary and secondary health-care costs all contribute to the quality of life and economic burden of herpes zoster and post herpetic neuralgia. To evaluate the potential impact of a zoster vaccination program in Canada, a thorough understanding of the Canadian specific burden of the disease and associated health-care resources is required. The purpose of this study was to measure the burden of illness, assess the impact on quality of life and determine the health-care resource utilization and cost associated with zoster and post herpetic neuralgia (severity and duration) in a Canadian sample.

Goal: This study will be a prospective cohort study of adults presenting with herpes zoster rash or zoster associated pain in the offices of community-based physicians and specialists across Canada. The objectives of this study are four fold:

- Measure the burden of illness due to zoster and post-herpetic neuralgia (severity and duration) in a Canadian sample;
- Assess the quality of life and quality adjusted life years (QALY) lost due to Zoster and PHN;
- Describe health-care resource utilisation associated with zoster and post-herpetic neuralgia in Canadian sample.
- Describe the direct and indirect costs per case of zoster and post-herpetic neuralgia in a Canadian sample.

Accomplishments: This is the only study evaluating a prospective cohort study of adults presenting with herpes zoster rash or zoster-associated pain in the offices of community-based physicians and specialists across Canada. The MASTER study has been able to provide data not presently available for characterizing the overall burden of zoster and post-herpetic neuralgia in Canada.

Impact: These estimates of health utilities have been used to assess the QALY lost associated with zoster and post-herpetic neuralgia and evaluate the cost-effectiveness of zoster/ post-herpetic neuralgia vaccination strategies. MASTER will be the first study to follow subjects up prospectively towards quantifying the health utilities lost associated with zoster and post-herpetic neuralgia and provide a clinical picture of the related burden of illness.

Publications:

Brisson M, Johnson RW, Levin MJ, Oxman MN, Schmader KE, Patrick DM, Koch C, Senecal M and Mansi JA. 2006. Measuring the pain and severity associated with the prodromal phase of herpes zoster (HZ) in Canada: A prospective

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continued

community-based study. 7th Canadian Immunization Conference, Winnipeg, Canada. December 3-6, 2006. (Oral Presentation)

Brisson M, Johnson RW, Levin MJ, Oxman MN, Schmader KE, Patrick DM, Koch C, Senecal M and Mansi JA. 2006. Measuring herpes zoster (HZ) and post-herpetic neuralgia (PHN) associated burden of illness, health care utilization and costs in Canada: A clinical epidemiological study. 7th Canadian Immunization Conference, Winnipeg, Canada. December 3-6, 2006. (Poster)

Brisson M, Johnson RW, Levin MJ, Oxman MN, Schmader KE, Patrick DM, Koch C, Senecal M, Mansi JA. 2006. Measuring the pain and severity associated with the prodromal phase of herpes zoster (HZ) in Canada: A prospective community based study. 13th Annual Meeting of the International Herpes Management Forum (IHMF), Prague, Czech Republic. October 27-29, 2006. (Oral Presentation)

Brisson M, Johnson RW, Levin MJ, Oxman MN, Schmader KE, Patrick DM, Koch C, Senecal M and Mansi JA. 2006. Measuring herpes zoster (HZ) and post-herpetic neuralgia (PHN) associated burden of illness, health care utilization and costs in Canada: A Clinical Epidemiological Study. 13th Annual Meeting of the International Herpes Management Forum (IHMF), Prague, Czech Republic. October 27-29, 2006. (Poster)

Directing vaccines toward a Th1 immune response

Need: Despite the identification of potential vaccine antigens for various infections, it is essential that the appropriate immune response is generated against these antigens. Both the adjuvant and route of immunization can have a profound effect on the immune response and efficacy of vaccination.

Goal: The goal is to use the well-established live *Leishmania* infection model in mice to characterize commercially available Toll-like receptor (TLR) agonists adjuvants and define the best site of immunization when using TLR adjuvants.

Accomplishments: We have established that TLR adjuvants can be used therapeutically in human clinical trials for existing cutaneous infections with *Leishmania*. We wish to now extend these observations to explore the use of these same TLR adjuvant to develop prophylactic immunological protection through directing the immune response toward a protective Th1 immune response, which is required to resolve *Leishmania* infections.

Impact: This research has the potential to significantly change the way vaccines are developed through focussing on the adjuvant. *Leishmania* is perhaps the best available live infection model to study vaccine adjuvant effects on Th1/Th2 and protective immunity. Moreover, our ongoing studies show that TLR adjuvants function much better when administered to the epidermis than to muscle tissue, which could also significantly change the future of vaccine delivery.

Publications:

Miranda-Verástegui C, Arévalo I, Llanos-Cuentas A, Ward B and Matlashewski G. 2005. Randomized, double-blind clinical trial of topical treatment 5% imiquimod (Aldara) with parental meglumine antimonate (Glucantime) in the treatment of cutaneous leishmaniasis in Peru Clin Inf Dis. 40:1395-1403.

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Supported by:

NIH NIAID (80%) to develop correlates of protection, NIH NIA (18%) to develop the assays, CIHR (1%) for the international collaboration.

Supported by:

NIH NIAID (100%)

T cell responses predict influenza risk in older adults

Need: There is an urgent need for more effective influenza vaccines, but antibody responses fail to predict vaccine failures. Thus, additional correlates of protection are needed.

Goal: The goal was to develop and validate a T cell assay as a surrogate of protection that could be used to identify the best candidate influenza vaccines to ultimately reduce influenza morbidity in older adults.

Accomplishments: Published the only paper to show that a T cell response correlates with protection in people. This assay of granzyme B has been developed exclusively in my laboratory in collaboration with Chris Bleackley.

Impact: The granzyme B assay is being validated across laboratories in Canada, US and Europe and will evaluate a proposed threshold level of granzyme B for use in large scale clinical trials of new influenza vaccines.

Publications:

McElhaney JE, Xie D, Hager WD, Barry MB, Wang Y, Kleppinger A, Ewen C, Kane KP and Bleackley RC. 2006. T cell responses are better correlates of influenza risk in the elderly. *J Immunol.* 176:6333-6339.

Adjuvants and virosomal vaccines for the elderly

Need: Despite widespread influenza vaccination programs in older adults, influenza-related hospitalizations and deaths continue to rise in older adults. There is an urgent need for more effective vaccines in older adults, but animal models have significant limitations for this purpose.

Goal: To develop *in vitro* methods using human peripheral blood mononuclear cells for pre-clinical testing of new

vaccines including viral antigen preparations and adjuvants to screen for the most effective combinations in older adults.

Accomplishments: Obtained a \$1.25M grant from NIH to develop this project in Canada. The project has been identified by the WHO for a collaboration with the researchers funded by the Gates Foundation to develop pandemic vaccines for the developing world.

Impact: This project will identify candidate influenza vaccines to move into Phase I clinical trials.

A strategy to optimize vaccine efficacy in older adults

Need: Testing of new vaccines in older adults largely depends on large-scale clinical trials measuring clinical outcomes in the absence of reliable surrogates of protection. Thus, new vaccines may advance to Phase III clinical trials before their real benefit can be assessed making this a very high-risk endeavour.

Goal: To adapt the assays of the cell-mediated immune response developed for influenza, to other vaccine preventable diseases including herpes zoster and respiratory syncytial virus.

Accomplishments: The assay of granzyme B and cytokines produced in zoster virus-stimulated peripheral blood mononuclear cells has now been adopted for a substudy of a large zoster vaccine trial as a correlate of protection against shingles.

Impact: The anticipated impact is that this assay will predict the degree and duration of protection from shingles following vaccination and will answer questions about vaccine benefits without having to repeat these large, expensive clinical trials.

Janet McElhaney
continued

Supported by:
Investigator Award from the Donaghue Foundation in Connecticut - had to be relinquished after one year when I returned to Canada. Merck Frosst Canada will sponsor the substudy of the vaccine trial.

Martin McGavin
Associate Professor
University of
Toronto
Sunnybrook Health
Science Centre

Supported by:
Sanofi-Aventis (66%)
and CIHR (33%).

Evaluation of a conserved cell-surface peptidyl prolyl-isomerase in Gram-positive pathogens as a potential vaccine antigen and target for attenuation of virulence

Need: Methicillin-resistant *Staphylococcus aureus* (MRSA) now causes more deaths than AIDS, and hypervirulent strains of MRSA have emerged in the community, known as Community Acquired MRSA that are notorious for causing severe invasive and frequently fatal infections in young otherwise healthy individuals. Hospital Associated MRSA has acquired resistance to all antimicrobial agents. Vaccines are urgently needed to control the spiraling morbidity and mortality that is attributed to *S. aureus* infections.

Goal: A cell-surface chaperone with prolyl isomerase function is essential for viability of *Bacillus subtilis*, and an orthologous gene together with the context of flanking genomic DNA is conserved in *S. aureus*. In *B. subtilis*, this gene PrsA functions as a chaperone to promote the folding of secreted proteins, and presumably to promote the proper folding of essential proteins that are involved in cell wall metabolism. We have proposed that PrsA and cell surface proteins that it chaperones, should constitute effective vaccine antigens for *S. aureus*.

Accomplishments: We have secured funding from CIHR and Sanofi-Aventis through the University-Industry Partnered Program. To date we have:

1. Constructed a conditional (ectopic expression) knockout of PrsA in *S. aureus*.
2. The *S. aureus* Pspac::prsA mutant remains viable in the absence of PrsA function, but is impaired in production of secreted proteins, and is attenuated in virulence.
3. We have purified PrsA to homogeneity, and obtained a crystal structure, which shows high resolution and conserved structure in the prolyl-isomerase domain, but is poorly resolved in the N-terminal domain. Consequently, we have initiated a search to find protein ligands (substrate proteins) that we hope will stabilize this domain.
4. We have conducted vaccination experiments, and the results were sufficiently encouraging that we have sent purified protein to

Sanofi-Aventis in France, trials are currently in progress in France for confirmation of our data.

5. We have used labeled PrsA protein to probe preparations of cell wall-associated proteins derived from *S. aureus*. We identified a protein that bound the labeled PrsA, and have cloned and expressed this protein. We have purified the recombinant protein and have confirmed that it is a ligand for PrsA. The protein has a domain that is implicated in cell wall metabolism, and is conserved in a family of *S. aureus* proteins.
6. We have requested an extension of funding from Sanofi, which has been verbally approved, so that we can:
 - i. Clone, express and purify other members of this protein family.
 - ii. Provide Sanofi with purified antigens to test in combination with PrsA as vaccine antigens.
 - iii. Characterize the biochemistry of the chaperone function of PrsA for this protein family, and initiate structural studies of protein complexes.

Impact: With preliminary encouraging results with PrsA and identification of protein ligands for PrsA, we are striding closer to being able to test novel vaccine formulations for prevention of severe *S. aureus* infections.

***Staphylococcus aureus* and atopic dermatitis**

Need: Approximately 10% of the Canadian population has atopic dermatitis, a chronically relapsing skin condition characterized by susceptibility to secondary skin infections, particularly by *Staphylococcus aureus*. Patients with atopic dermatitis are nearly always heavily colonized by *S. aureus*, not just in the nares (nose) which is considered the natural habitat, but also on the exposed skin. Patients with atopic dermatitis should be at risk of colonization and infection by severe invasive community acquired MRSA.

Goal: This project is not directly related to vaccine development, but we have proposed that understanding the association of *S. aureus* with atopic dermatitis patients may ultimately assist in vaccine formulation.

Martin McGavin
continued

Supported by:
Canadian
Dermatology
Foundation. Have
applied to the CIHR
Catalyst Grant
Program, Skin
Diseases and
Conditions

This is because:

1. Patients with severe atopic dermatitis are nearly always heavily colonized by *S. aureus*.
2. Much of this may be explained by atopic dermatitis patients having an altered cytokine profile that favors Th2 at the expense of Th1, i.e. a stronger Th2/Th1 ratio.
3. This favours stronger humoral immunity, but weaker cellular immunity, consequently atopic dermatitis patients are also more susceptible to viral infections.
4. We propose that the persistence of *S. aureus* on the atopic dermatitis skin could be a function of intracellular persistence, favoured by the weakened Th1 response.
5. We also speculate that the chronic infections with stronger Th2 response provides a strong humoral immune response towards *S. aureus* antigens, which may actually protect against severe invasive infections.
6. Consequently, we would like to initiate a discovery-based program to identify *S. aureus* secreted and cellular antigens that are prominently recognized by antibodies from atopic dermatitis patients.

Accomplishments: We have screened a cohort of 43 mostly adult patients with severe atopic dermatitis, and have identified and genotyped *S. aureus* from all patients. One patient has remained colonized by a suspected “hyper-virulent” lineage of *S. aureus* for more than one year. Three other patients for which strains were collected on follow-up visits separated by 4 or 5 months have also remained colonized by the same strain. This is in spite of treatment with anti-inflammatory and antimicrobial agents. We are in the process of collecting strains from several other patients among the original cohort to assess the stability of colonization. If our hypothesis is correct, the weakened cellular immunity may encourage intracellular persistence such that the patients remain colonized by the same strain.

Impact: Using a discovery-based proteomics approach, we hope to identify a profile of cell surface and secreted antigens that may be useful as vaccine antigens to protect against severe invasive infection.

Retro-inversion advances the therapeutic potential of host defence peptides through reduced toxicity, increased stability and conserved biological activity

Goal: The ability of host defense peptides (HDP) to induce protective innate immune responses while dampening pathological inflammation makes them highly attractive as antimicrobials. While employed as topical treatments, their systemic administration has been limited by their prohibitive costs and potential toxicity. Retro-inversed (RI) peptides, in which the sequence is reversed and the chirality of each amino acid inverted, are predicted to maintain the same structure and biological activity as their natural counterparts but resist proteolytic degradation. Improved biological stability could improve the therapeutic potential of HDPs by reducing required dose quantities to minimize costs and dose-dependent toxicity.

Accomplishments: We report that the RI isomer of BMAP28 presents a conserved structure, is resistant to proteolytic degradation and has improved antimicrobial activity. Additionally, RI-BMAP28 maintains both immunomodulatory and anti-endotoxin capabilities as physiological concentrations of the peptide modulate inflammation at the levels of gene expression and cytokine release in LPS-stimulated monocytes and peripheral blood mononuclear cells respectively. An unexpected but highly desirable outcome is a dramatic reduction of cytotoxicity, independent of reduced doses, for RI-BMAP28 apparently due to reduced uptake or association with susceptible host cells. A similar reduction in toxicity was observed with other RI-HDP. These improved *in vitro* characteristics have therapeutic significance as RI-BMAP28 is more effective than BMAP28 in protecting mice in a *Salmonella* intraperitoneal challenge model.

Impact: Retro-inversion significantly advances the therapeutic value of BMAP28 and may offer similar benefit for other HDP.

Scott Napper
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Vaccine and Infectious
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Supported by:

The Advancing Canadian
Agriculture and Agri-Food
Program (50%), Bill and
Melinda Gates Foundation
(50%).

Peter A Newman
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Work/Centre for Applied
Social Research
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Supported by:
CIHR Institute of Gender and
Health

Promoting equity in access to HIV vaccines among black women in Canada (Sisters, Mothers, Daughters and Aunties)

Need: Canadian black women are at disproportionate risk for HIV infection. An HIV vaccine would be a tremendous asset. Over 2 decades into the epidemic, the main prevention technology—the male condom—is ultimately under the control of men. Nevertheless, a variety of issues and barriers may delimit access and acceptability of future HIV vaccines.

Goal: To assess HIV vaccine acceptability among black women, to identify determinants of HIV vaccine acceptability, and to explore existing obstacles to HIV prevention.

Accomplishments: We completed a two-stage project: 1) 4 focus groups and 6 key informant interviews with diverse black women recruited from community venues, 2) a survey of 206 black women in the GTA to assess HIV vaccine acceptability.

Impact: In addition to professional journal publications, we are in an ongoing process of disseminating findings to the community through a booklet, agency contacts and community forums.

Publications:

Newman PA, Williams CC, Massaquoi N, Brown M and Logie C. 2008. HIV prevention for black women: Structural barriers and opportunities. *Journal of Health Care for the Poor and Underserved*, in press.

Williams CC, Newman PA, Massaquoi N, Brown M and Sakamoto I. 2008. HIV prevention and the social organization of risk for Black women in Canada. *Social Science & Medicine*, in revision.

HIV vaccine trials and community engagement

Need: HIV vaccine trials will require tens of thousands of volunteers over the coming decades. The experiences of trial volunteers and community perceptions of HIV vaccine trials are likely to influence future availability of “high-risk” volunteers.

Goal: To assess social consequences of HIV vaccine trial participation, to monitor HIV risk behaviours among trial participants, and to engage and prepare communities for future HIV vaccine trials

Accomplishments: Successfully partnered with the Toronto site of the STEP study, collected longitudinal data over the course of the trial, conducting community focus groups to explore reactions to the trial.

Impact: Will provide an understanding of community and participant reactions in response to the STEP study, in which the vaccine may have increased vulnerability to HIV infection, and will provide an empirical basis for the design of interventions to facilitate future trial recruitment, to support ethical and transparent HIV vaccine trials, and data to support knowledge translation activities during and after HIV vaccine trials.

Publications:

Newman PA, Daley A, Halpenny R and Loutfy M. 2008. Community heroes or “high-risk” pariahs? Reasons for declining to enroll in an HIV vaccine trial. *Vaccine* 26:1091-1097.

Peter A Newman
continued

Supported by:
Ontario HIV Treatment Network (90%) and a pilot grant from University of California, Los Angeles (10%).

Peter A Newman
continued

Supported by:

National Institute of Mental
Health

Post-trial HIV vaccines: receptivity, risk and disparities

Need: HIV vaccines represent the greatest hope for ending the epidemic. Nevertheless, existing health-care disparities are likely to be reproduced with HIV vaccines absent proactive intervention.

Goal: To assess HIV vaccine acceptability among a probability sample of vulnerable adults in Los Angeles, to identify factors associated with HIV vaccine acceptability.

Accomplishments: Completed a probability sample survey of 1306 vulnerable adults in Los Angeles.

Impact: Several manuscripts in progress. May inform health policy and interventions to increase access and acceptability for future HIV vaccines and other biomedical innovations.

Publications:

Newman PA, Duan N, Kakinami L and Roberts K. 2008. What can HIV vaccine trials teach us about dissemination? *Vaccine* 26:2528-2536.

Kakinami L, Newman PA, Roberts K and Duan N. 2008. Differences in HIV vaccine acceptability between genders. *AIDS Care* 20:542-546.

Newman PA, Seiden D, Roberts K and Duan N. 2007. A small dose of HIV? HIV vaccine mental models and risk communication. *Health Education & Behavior*, Prepublished: <http://www.ncbi.nlm.nih.gov/pubmed/18032589?dopt=Citation>

Newman PA, Duan N, Lee S-J, Rudy ET, Seiden D, Kakinami L and Cunningham WE. 2007. Willingness to participate in HIV vaccine trials among communities at risk: The impact of trial attributes. *Preventive Medicine* 44:554-557.

Assessment of vaccine coverage of pre-school children in Nova Scotia: The Nova Scotia vaccine coverage study (NS-VaCS)

Need: The success of an immunization program is reflected not only by the reduction in the number of newly diagnosed cases of a vaccine-preventable disease but also through the optimization of vaccine coverage for that disease in the population. There is currently no reliable information on vaccination rates for children in Nova Scotia. Without these data, it is difficult to evaluate the success of any immunization program.

Accomplishments: This project has recently started. Research instruments for the collection and analysis of vaccine data from administrative health databases and public health records have been developed. A questionnaire survey methodology has been developed and piloted and will be used to compare data derived from these sources with parental knowledge of their children's vaccinations, as well as identifying information on knowledge, attitudes and opinions with respect to vaccinations.

Impact: In consideration of the national targets established for immunization of pre-school children, it is essential to gain an understanding of the current vaccine coverage of these children. The outcomes of this project will enable a better understanding of vaccine completeness and uptake in Nova Scotia, provide information to help ensure that vaccination uptake of pre-school children of vaccines outlined in the NS immunization schedule is as complete as possible, and identify potential influences on heterogeneity in vaccine uptake.

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Supported by:

Nova Scotia Department of
Health Promotion and
Protection

Girish B Patel
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and Group Leader
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Group
Institute for Biological
Sciences
National Research Council
of Canada

Supported by:

National Research Council of
Canada (2005 - continuing)
and DowAgro Sciences
(2005 - 2007).

**Development of novel, non-replicating, mucosal adjuvants
and mucosal vaccine delivery systems**

Need: Most pathogens invade the mammalian host through the mucosal surfaces (respiratory, gastrointestinal, reproductive tract, urinary tract). Elicitation of immunity at the mucosal sites would help prevent attachment of pathogens, diseases at mucosal sites and progression to systemic infection in other organs. Mucosal immunity also helps toxin neutralization. Current vaccines administered via systemic routes do not elicit much immune response at mucosal surfaces.

Goal: To develop self-adjuvanting mucosal vaccine delivery using archaeal polar lipids. This is a relatively new project, started in 2005.

Accomplishments: Demonstrated that archaeal lipid mucosal adjuvant and vaccine delivery technology is highly efficient in eliciting long-lasting mucosal and systemic immune responses upon intranasal vaccination of mice.

Impact: The technology is being evaluated for applications in human and veterinary vaccines. Currently there are no non-replicating mucosal vaccines approved for use in humans.

Publications:

Patel GB, Zhou H, Ponce A and Chen W. 2007. Mucosal and systemic immune responses by intranasal immunization using archaeal lipid-adjuvanted vaccines. *Vaccine* 25:8622-8636.

T cells targeted against a single minor histocompatibility antigen can cure solid tumours

Need: To develop effective cancer vaccines.

Goal: To determine whether and how T cells primed against a single epitope can eradicate solid tumours.

Accomplishments: We report that injection of CD8 T cells primed against the H7a Ag can cure established melanomas in mice. Tumour rejection was initiated by preferential extravasation at the tumour site of interferon-gamma producing H7a-specific T cells. Intratumoural release of interferon-gamma had two crucial effects: inhibition of tumour angiogenesis and upregulation of class I major histocompatibility complex (MHC) expression on tumour cells that thereby became more susceptible to killing by CD8 T-cell granule exocytosis. Despite ubiquitous expression of H7a, dissemination of a few anti-H7a T cells in extralymphoid organs did not cause graft-versus-host disease nor vitiligo because host nonhematopoietic cells were protected by their low class I MHC expression.

Impact: To perform a clinical trial to test our strategy in humans.

Publications:

Meunier MC, Delisle JS, Bergeron J, Rineau V, Baron C and Perreault C. 2005. T cells targeted against a single minor histocompatibility antigen can cure solid tumors. *Nat Med.* 11:1222-1229.

Discovery of tumour-specific antigens presented by MHC I molecules

Need: To develop effective cancer vaccines.

Goal: To discover peptides expressed at high levels in both primary tumours and metastases.

Claude Perreault
Professor
Université de Montréal
(IRIC)

Supported by:

National Cancer Institute of
Canada, Canadian Cancer
Society, Terry Fox
Foundation

Claude Perreault
continued

Accomplishments: Together with the group of P. Thibault (Canada Research Chair in Proteomics and Bioanalytical Spectrometry), we developed a novel high-throughput mass spectrometry approach that yields an accurate definition of the nature and relative abundance of unlabeled peptides presented by MHC I molecules. We identified 189 and 196 MHC I-associated peptides from normal and neoplastic mouse thymocytes, respectively. By integrating our peptidomic data with global profiling of the transcriptome, we reached two conclusions. The MIP repertoire of primary mouse thymocytes is biased toward peptides derived from highly abundant transcripts and is enriched in peptides derived from cyclins/cyclin-dependent kinases and helicases. Furthermore, we found that about 25% of MHC I-associated peptides were differentially expressed on normal versus neoplastic thymocytes. About half of those peptides derived from molecules directly implicated in neoplastic transformation (e.g. components of the PI3K-AKT-mTOR pathway). In most cases, overexpression of MHC I peptides on cancer cells entailed posttranscriptional mechanisms. Our results show that high-throughput analysis and sequencing of MHC I-associated peptides yields unique insights into the genesis of the MIP repertoire in normal and neoplastic cells.

Impact: Our novel strategy should allow us to generate a global portrait of tumour antigens expressed on human cancer cells.

Publications:

Fortier MH, Caron E, Hardy MP, Voisin G, Lemieux S, Perreault C and Thibault P. 2008. The MHC I immunopeptidome is moulded by the transcriptome and conceals a tissue-specific signature. *J Exp Med.* 205:595-610.

Abundance and diversity of HER-2/NEU peptides presented by MHC class I molecules in antigen presenting cells and breast cancer

Need: To develop effective vaccines for breast cancer.

Goal: To develop effective vaccines for breast cancer.

Accomplishments: Under the leadership of J. Bramson (McMaster University), researchers from Ontario, Quebec and British Columbia have created a Cancer Immunotherapy Program.

Impact: To generate novel strategies for translational research in breast cancer immunotherapy.

Claude Perreault
continued

Supported by:
NCIC, Terry Fox Foundation

Andrew Potter
Director
Vaccine and Infectious
Disease Organization

Supported by:

NSERC (35%), CIHR (10%),
NCE-CBDN (10%), ALIDF
(5%), BIDF (5%), Industry
(35%)

Vaccines for the prevention of zoonotic infections from food-producing animals

Need: The transmission of disease from animals to humans has become a major source of infection in Canada, particularly in high-risk populations. At the present time, there are few methods for the control of these diseases. We believe that vaccination of both the animal and human populations will have a significant impact on environmental safety (i.e. Walkerton-type outbreaks), foodborne illness and travellers' diarrhea.

Goal: The goal of the project is to produce a comprehensive family of vaccines for zoonotic pathogens that can be used in animals to lessen the environmental load of these organisms, and in humans to prevent disease in high-risk populations.

Accomplishments: A vaccine for *Escherichia coli* O157:H7 was developed in collaboration with Dr. Brett Finlay and transferred to the private sector for commercialization. Protective antigens from *Salmonella* spp and *Campylobacter jejuni* have been identified, and we are currently working on the development of oral and intranasal formulations using novel adjuvants and immunomodulators. While the *E. coli* vaccine was designed for use in animals, the *C. jejuni* vaccine will be used for vaccination of both animal reservoirs as well as humans.

Impact: This is the first example in Canada of a technology designed to reduce the threat of human disease based upon treatment of the animal reservoir (other than rabies). The technology has been transferred to the private sector for commercial development, and we anticipate widespread application within 2 years in Canada.

Publications:

Asper D I, Sekirov B, Finlay B, Rogan D and Potter A. 2007.

Cross reactivity of enterohemorrhagic *Escherichia coli* O157:H7-specific sera with non-O157 serotypes. *Vaccine* 25:8262-8269.

Babiuk S, Asper D, Rogan D, Mutwiri G and Potter AA. 2008. Subcutaneous and intranasal immunization with type III secreted proteins can prevent colonization and shedding of *Escherichia coli* O157:H7 in mice. *Microbial Pathogenesis*, in press.

Biswas D, Fernando UM, Reiman CD, Willson PJ, Townsend HG, Potter AA and Allan BJ. 2007. Correlation Between *In Vitro* Secretion of Virulence-Associated Proteins of *Campylobacter jejuni* and Colonization of Chickens. *Curr Microbiol.* 54:207-212.

Fernando U, Biswas D, Allan B, Attah-Poku S, Willson P, Valdivieso-Garcia A and Potter AA. 2008. Serological assessment of synthetic peptides of *Campylobacter jejuni* NCTC11168 FlaA protein using antibodies against multiple serotypes. *Medical Microbiology and Immunology*, in press.

Potter AA, Klashinsky S, Li Y, Frey E, Townsend H, Rogan D, Erickson G, Hinkley S, Klopfenstein T, Moxley RA, Smith DR and Finlay BB. 2004. Decreased shedding of *Escherichia coli* O157:H7 by cattle following vaccination with type III secreted proteins. *Vaccine* 22:362-369.

Vaccines for protein-folding disorders

Need: Protein folding disorders include a growing number of diseases that contribute significantly to health-care costs associated with chronic disease as well as perceived public health risks. The latter includes prion-mediated diseases that have a proven link to food and environment (e.g. bovine spongiform encephalopathy) or a potential link (e.g. Chronic Wasting Disease). At the present time, there is no significant therapy for such diseases.

Andrew Potter
continued

Supported by:
PrioNet Canada (50%),
Sask ADF (50%)

Andrew Potter
continued

Goal: The goal of this project is to develop vaccines for a variety of protein folding disorders based upon immunization with novel exposed epitopes on the aberrant form of the respective protein. We have developed a novel carrier system for the generation of immune responses against these antigens and will use this in combination with epitopes identified by Dr. Neil Cashman, UBC/PrioNet for both prophylactic and therapeutic immunization as well as the generation of specific serological therapeutic antibodies.

Accomplishments: We have successfully generated immune responses in animals against the misfolded Prion protein, PrP^{Sc}, which do not cross react with the native form of the protein. Given the conserved nature of the exposed epitopes, this should be a broadly cross reactive vaccine which will be applicable to most prion-mediated diseases. We are currently in the process of extending this to include other targets and diseases such as amyotrophic lateral sclerosis. In addition to this, in collaboration with researchers in the US, we are using this vaccine to generate large quantities of polyclonal antisera in humanized cattle as a potential therapeutic reagent.

Impact: The generation of sustained, specific immune responses against misfolded forms of self proteins has been problematic in the past. We have successfully developed a carrier system for the generation of such responses which will have application for the generation of both therapeutic vaccines as well as therapeutic reagents for a variety of chronic disorders.

Modeling HPV Vaccine Strategies in British Columbia

Need: Given limited resources, it is important to design an effective and cost-effective vaccination program by understanding the transmission dynamics of the pattern of disease spread and identifying the priority groups that are eligible to receive a new vaccine product.

Goal: The objective of this project was to develop a mathematical dynamic model to study the transmission dynamics of HPV infection among the sexually-active population in British Columbia and to assess the impact of various vaccination strategies on reducing the burden of disease.

Accomplishments: This undertaking was entirely unique in that it was the first time that a public health agency conducted a quantitative analysis on the impact of various vaccination strategies on the spread of HPV (independent of pharmaceutical companies). The model outcomes were used in policy-making discussions.

Impact: The results from this project helped in shaping the vaccination program at the provincial and national level. This project created the infrastructure to develop mathematical models to evaluate the impact of existing and new immunization programs for the purpose of policy recommendation in a timely manner.

Publications:

Gunther P, Ogilvie G, Naus M, Young E, Patrick DM, Dobson S, Duval B, Noel PA, Marra F, Miller D, Brunham RC and Pourbohloul B. 2008. Protecting the next generation: What is the role of the duration of HPV vaccine immunity? *Journal of Infectious Diseases*, in press.

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**BC Centre for Disease
Control**

Supported by:

British Columbia Ministry of
Health (100% support)

Babak Pourbohloul
continued

Supported by:
CIHR, BC Ministry of Health

Modeling Pandemic Influenza Preparedness Strategies in British Columbia

Need: Since an effective vaccine against a pandemic strain of influenza may not be available at the onset of a global pandemic, it is crucial to evaluate the impact of different vaccination strategies to stop the spread of pandemic flu, prioritize target groups and assess the impact of the delay in vaccine production on the transmission dynamics.

Goal: To evaluate the impact of vaccination, in combination with other contact- and/or transmission-reducing intervention measures, to stop the spread of pandemic flu and assess the impact of the delay in vaccine production for the new strain on the transmission dynamics

Accomplishments: We have developed a new analytical/computational methodology for rapid assessment of vaccination program outcomes during epidemic/pandemic events.

Impact: This project will provide scientific input in the decision-making process for pandemic preparedness in British Columbia. Also, it has become the basis for an international collaboration on pandemic preparedness.

Publications:

Bansal S, Meyers LA and Pourbohloul B. 2006. A comparative analysis of influenza vaccination programs. *PLoS Med.* 3:e387.

Development of an inner-core lipopolysaccharide (LPS)-based conjugate vaccine to prevent *Neisseria meningitidis* invasive disease (a collaborative project also involving researchers at Oxford University and industry)

Need: Despite the success of licensed meningococcal group C vaccine (one of which was developed at NRC) in protecting infants from group C disease, and the recent launch of tetravalent vaccines for children (against groups A, C, W-135 and Y), there is still no effective vaccine available to provide protection against Group B meningococcal disease, which remains a significant threat in the developed world.

Goal: The research team has devised and is developing a LPS-based conjugate vaccine platform technology as a candidate vaccine for providing protection against, not only Group B meningococcal disease, but as a second generation vaccine against all meningococcal groups.

Accomplishments: The researchers have demonstrated proof-of-concept and have entered into research and technology transfer agreements with a major vaccine developer to further develop the concept and to bring it to the stage of clinical development.

Impact: The successful outcome of this project will result in clinical development of an effective vaccine to protect children against all disease-causing meningococcal groups. This will save lives and reduce health-care costs in Canada.

Publications:

Cox AD, Wright JC, Gidney MAJ, Lacelle S, Plested JS, Martin A, Moxon ER and Richards JC. 2003. Identification of a novel inner core oligosaccharide structure in *Neisseria meningitidis* lipopolysaccharide. *Eur J Biochem.* 270:1759-1766.

Gidney MA, Plested JS, Lacelle S, Coull PA, Wright JC, Makepeace K, Brisson JR, Cox AD, Moxon ER and Richards JC. 2004. Development characterization and functional activity of a panel of specific monoclonal antibodies to inner core lipopolysaccharide epitopes in *Neisseria meningitidis* *Infect Immun.* 72:559-569.

Jim Richards
Director General
Institute for
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National Research
Council of Canada

Supported by:

NRC A-base funding (~30%), Wellcome Trust (UK) (~15%), Medical Research Council (UK) (~20%), Industry (30%).

Kenneth L Rosenthal
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Supported by:

CIHR, CANVAC, OHTN,
Bill and Melinda Gates
Foundation

Development of mucosal vaccines for sexually transmitted infections

Need: Despite the fact that the vast majority of infections globally are initiated at mucosal surfaces of the body, we have not exploited this route of vaccine delivery, in part, due to limited understanding of mucosal innate and adaptive immune responses, how to optimally induce mucosal responses and the challenges in assessing these responses. Recent findings indicating that HIV, the worst epidemic in human history, is a mucosally transmitted infection of the mucosal immune system and recent failures of conventional vaccine approaches is spurring a new drive to better understand and evaluate mucosal vaccines and immune responses.

Accomplishments: We were among the first groups to demonstrate that recombinant adenovirus vectors delivered intranasally induced strong, long-lasting adaptive immune responses in the genital tract of mice that protect against lethal intravaginal (IVAG) herpes simplex virus-2 (HSV-2) infection. Indeed, we demonstrated that adaptive immune responses compartmentalized to the mucosa or systemic immune systems dependent on the route of immunization and the time following vaccination. More recently we also showed that intrarectal immunization induced potent protection against IVAG HSV-2. Although the genital mucosa has been considered a non-immune inductive site, especially with non-replicating antigens, we showed that IVAG immunization with recombinant glycoprotein B of HSV-2 when mixed with CpG DNA as an adjuvant, induced immunity and protection against IVAG HSV-2 challenge. We have also shown that induction of anti-viral CTL in the mucosa is stronger and longer lasting following mucosal versus parenteral vaccination and that memory CD8⁺ T-cells persist in the tissue sites, as opposed to the lymph nodes following immunization. We have also gone on to evaluate various Toll-like receptor ligands as mucosal vaccine adjuvants and using laser capture microscopy and a

quantitative RT-PCR, we have characterized the effect of the estrous cycle on TLR expression in the epithelium of the murine female genital tract. Most recently, we are developing mucosal vaccines that induce both cellular and humoral immunity, especially secretory IgA against HIV-1 and we recently developed a humanized mouse model and used it to demonstrate that mucosal immunization and challenge induced human innate and adaptive mucosal immune responses.

Impact: Based on our pre-clinical investigations, we are well positioned to move forward with increased focus on human-based mucosal studies (see below) and participate in development of a clinical program aimed at developing and testing various mucosal vaccine platforms.

Publications:

Gallichan WS, Woolstencroft RN, Guarasci T, McCluskie MJ, Davis HL and Rosenthal KL. 2001. Intranasal immunization with CpG oligodeoxynucleotides as an adjuvant dramatically increases IgA and protection against herpes simplex virus-2 in the genital tract. *J Immunol.* 166:3451-3457.

Ashkar AA, Bauer S, Mitchell WJ, Vieira J and Rosenthal KL. 2003. Local delivery of CpG oligodeoxynucleotides induces rapid changes in the genital mucosa and inhibits replication, but not entry, of herpes simplex virus type 2. *J Virol.* 77:8948-8956.

Kwant A and Rosenthal KL. 2004. Intravaginal immunization with viral subunit protein plus CpG oligodeoxynucleotides induces protective immunity against HSV-2. *Vaccine* 22:3098-3104.

Gill N, Rosenthal KL and Ashkar AA. 2005. NK and NKT cell-independent contribution of Interleukin-15 to innate protection against mucosal viral infection. *J Virol.* 79:4470-4478.

Kenneth L Rosenthal
continued

Kenneth L Rosenthal
continued

Supported by:
Bill and Melinda Gates
Foundation, OHTN, CIHR

Zhu Q, Thomson CW, Rosenthal KL, McDermott MR, Collins SM and Gaudie J. 2008. Immunization with adenovirus at the large intestinal mucosa as an effective vaccination strategy against sexually transmitted viral infection. *Mucosal Immunol.* 1:78-88.

Role of innate and mucosal immunity in the pathogenesis of, and resistance to, HIV infection and development of optimized assays to evaluate mucosal innate and adaptive immune responses

Need: The role and importance of innate immune responses was overlooked for decades in immunology. With the discovery that our innate immune system utilizes evolutionarily conserved pattern recognition receptors, such as the Toll-like receptors (TLRs), to almost immediately detect and respond to infection has had remarkable effects on our understanding of pathogenesis and immunity to infections. With renewed interest in innate immunity and its importance in shaping adaptive immune responses, there is an urgent need to better understand the role of innate immunity in viral infections, particularly HIV, and how viruses manipulate innate immune responses. Furthermore, a major barrier to development of mucosal vaccines is the lack of standardized, optimized assays to evaluate mucosal innate and adaptive immune responses.

Accomplishments: We were among the first groups to demonstrate the use of TLR ligands, such as CpG oligodeoxynucleotides, as effective mucosal vaccine adjuvants. Indeed, we went on to demonstrate that innate ligands/agonists when delivered alone directly to the genital mucosa could protect female mice against a lethal intravaginal infection with HSV-2. We have gone on to develop precise methods to measure expression of all mouse and human TLRs and other PRRs (e.g. RIG-I and Mda5). Recently, we demonstrated that expression and responsiveness of select

TLRs is significantly increased in HIV-1 infection in humans and correlates with virus load. Indeed, there is progressive dysfunction of innate immune sensing in HIV infection that appears to be directly driven by the virus and leads to profound immune activation that underlies the pathogenesis of HIV disease progression. Most recently, as part of our Gates Grand Challenge studies with Dr. Plummer *et al.*, we showed that cervical mononuclear cells isolated from the genital tracts of HIV-resistant commercial sex workers have significantly lower expression and responsiveness of their TLRs versus HIV susceptible women. Thus, resistance to HIV infection may reflect a dampened down innate response following mucosal exposure to virus.

As part of our involvement in the Collaborations for AIDS Vaccine Development, we are engaged in studies aimed at developing more precise ways of measuring innate and adaptive mucosal immune responses.

Impact: Our studies are leading to a better understanding of resistance to and pathogenesis of HIV infection. We anticipate that studies aimed at developing and improving assays to measure innate and adaptive mucosal responses will facilitate vaccine development and testing. Indeed, we would hope to play a key role in assessing mucosal responses following vaccination.

Publications:

Dumais N, Patrick A, Moss RB, Davis HL and Rosenthal KL. 2002. Mucosal immunization with inactivated human immunodeficiency virus plus CpG oligodeoxynucleotides induces genital immune responses and protection against intravaginal challenge. *J Infect Dis.* 186:1098-1105.

Leith JG, Clark DA, Matthews TJ, Rosenthal KL, Luscher MA, Barber BH and MacDonald KS. 2003. Assessing human alloimmunization as a strategy for inducing HIV Type 1

Kenneth L Rosenthal
continued

Kenneth L Rosenthal
continued

neutralizing anti-HLA responses. *AIDS Res Hum Retroviruses* 19:957-965.

Jiang JQ, Patrick A, Moss RB and Rosenthal KL. 2005. CD8⁺ T-cell-mediated cross-clade protection in the genital tract following intranasal immunization with inactivated human immunodeficiency virus antigen plus CpG oligodeoxynucleotides. *J Virol.* 79:393-400.

Rosenthal KL. 2007. Chapter 9. Alternate routes on the roadmap to an HIV vaccine: Importance of innate and adaptive mucosal immunity. In: *AIDS Vaccine Development: Challenges and Opportunities*. Ed: W Koff, P Kahn & ID Gust, International AIDS Vaccine Initiative, NY & Univ. of Melbourne, Australia, Feb. 2007.

Lester RT, Yao X-D, Ball TB, McKinnon LR, Kaul R, Wachihi C, Jaoko W, Plummer FA and Rosenthal KL. 2008. Toll-like receptor expression and responsiveness are increased in viraemic HIV-1 infection. *AIDS* 22:685-694.

Study of the mechanisms involved in local reactions to childhood booster vaccinations

Need: While acellular pertussis-based combination vaccines for infants and young children substantially decreased the frequency of systemic adverse reactions, they did not solve the problem of increasingly frequent and severe local reactions to booster doses, especially the second booster given to pre-school children. About 25% of such vaccinees experience large local reactions, with ≥ 5 cm redness or swelling. While well tolerated, these reactions are undesirable in a climate of increasing public concern about vaccine safety.

Goal: The CIHR-funded trial sought to determine the rate of local reactions in the first cohort of children to present for a 5th consecutive dose of DTaP vaccine and to determine if a modified vaccine (Tdap) reduced the frequency of reactions. The roles of antibodies and cellular immunity to vaccine antigens as potential causes of local reactions were explored.

Accomplishments: The study showed a somewhat lower rate of large reactions (≥ 5 cm, 16%) than described in pre-licensure studies. The modified vaccine substantially reduced but did not eliminate large reactions. Cell-mediated immunity to vaccine antigens was more often present than antibodies prior to booster vaccination, suggesting that local reactions may be driven by persistent cell-mediated immunity. Delaying boosters until later in childhood and using modified formulations could minimize local reactions.

Impact: The study provides a rationale for preferring a modified vaccine for pre-school boosters, when a Tdap-IPV vaccine is available.

Publications:

Scheifele DW, Halperin SA, Ochnio JJ, Ferguson AC and Skowronski DM. 2005. A modified vaccine reduces the rate of

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Supported by:

CIHR (75%), sanofi pasteur
(25%)

David Scheifele
continued

Supported by:
Shire Biologics

large injection site reactions to the preschool booster dose of diphtheria-tetanus-acellular pertussis vaccine – results of a randomized, controlled trial. *Pediatr Infect Dis J.* 24:1059-1066.

Evaluation of the potential for a Canadian-made influenza vaccine to cause oculorespiratory syndrome

Need: An influenza vaccine produced in Quebec in 2000 caused a new phenomenon of “oculorespiratory syndrome” to occur at an appreciable rate. The vaccine formulation for the following year was revised but needed to be rapidly evaluated for safety.

Goal: The goal was to rapidly evaluate the first available lot of vaccine in 2001 for safety, especially the potential to cause oculorespiratory syndrome. Failure to complete the study on schedule or finding a safety concern would have stopped vaccine distribution, causing a nationwide vaccine shortage.

Accomplishments: The double-blind cross-over design worked extremely well, enabling the study to be completed in only 6 weeks, from initial recruitment to preliminary report. No safety concern was identified, permitting approval for sale of the vaccine production and avoiding shortages. The design yielded one of the most accurate safety assessments ever undertaken. The CAIRE network of trial centres that carried out the study (in Vancouver, Calgary, Winnipeg and Quebec City) faced pressures and timelines approximating those of a pandemic influenza situation.

Impact: A nationwide shortage of vaccine was avoided and the reputation of Canada’s only domestic vaccine manufacturer was restored.

Publications:

Scheifele DW, Duval B, Russell ML, Warrington R, De Serres G, Skorwonski DM, Dionne M, Kellner J, Davies D and

MacDonald J. 2003. Ocular and respiratory symptoms attributable to inactivated, split influenza vaccine: evidence from a controlled trial involving adults. *Clin Infect Dis.* 36:850-857.

Skowronski DM, De Serres G, Scheifele D, Russell ML, Warrington R, Davies HD, Dionne M, Duval B, Kellner J and MacDonald J. 2003. Randomized, double-blind, placebo-controlled trial to assess the rate of recurrence of oculorespiratory syndrome following influenza vaccination among persons previously affected. *Clin Infect Dis.* 37:1059-1066.

Scheifele D, Duval B, De Serres G and Skowronski DM. 2003. Unique roles of a data and safety monitoring board in vaccine safety trials with compressed timelines and urgent implications. *Control Clin Trials* 24:99-104.

David Scheifele
continued

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Supported by:
CIHR

Development of broad-spectrum vaccine based on conserved functional domains of bacterial transferrin receptors

Need: Antigenic variation and natural transformation of the host-adapted bacterial species will enable the bacteria to continue to evade conventional vaccines.

Goal: To develop broad-spectrum vaccines against determinants that cannot change.

Accomplishments: Have demonstrated that the sites of interaction are conserved. Proof-of-concept experiments demonstrating immunogenicity in humans and ability to induce a cross-protective response have been completed.

Impact: If our proposed approaches are successful it could lead to a broad-spectrum vaccine against several pathogens that could not be overcome by mutation or exchange.

Publications:

Proof-of-concept experiments have not been published as they are being included in a CIP.

Positional cloning of genes that impact on anti-mycobacterial immune responsiveness

Need: The host genetic background provides the blueprint for the effectiveness of vaccine-induced immunity. Yet, little is known about the allelic variants governing vaccine responsiveness.

Goal: The overall objective is to identify genetic determinants that govern anti-mycobacterial immune reactivity in several critical anti-mycobacterial immune assays among children living in a high *M. tuberculosis* exposure setting.

Accomplishments: Employing genome scanning and high resolution linkage disequilibrium mapping several major genetic host factors with a strong impact on immune reactivity have been identified.

Impact: These results suggest that efficacious TB vaccination strategies will need to take the host genetic background into consideration.

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Supported by:
CIHR, AERAS Foundation,
Sequella Foundation

Jamie Scott
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Supported by:
NIH

Peptide vaccines to elicit HIV-1-neutralizing antibodies

Need: There are no effective vaccines to protect against HIV-1 infection. Neutralizing antibodies can protect against SHIV and HIV infection in animal models. Thus development of vaccines that elicit neutralizing antibodies is a priority in HIV vaccine research.

Goal: The goal was to develop peptides that bind tightly to broadly neutralizing monoclonal antibodies against HIV-1, to study their binding properties and structure in complex with Fab, and to test them as immunogens that may elicit Env-binding and broadly neutralizing antibodies.

Accomplishments: Tight binding peptides were developed for MAbs b12, 2G12, 4E10 and 2F5, bound structures were solved for b12 and 2G12, but not yet for 2F5 and 4E10 peptides. Immunization with peptides for b12 and 2G12 did not elicit Env-crossreactive Abs, but immunization with 2F5 and 4E10 peptides did. Abs against the 4E10 peptide were weakly neutralizing.

Impact: MAbs 4E10 and 2F5 bind linear epitopes on gp41, perhaps in the context of the viral membrane. Our optimized peptides may mimic the structure of these epitopes, particularly when presented on the phage surface.

Publications:

Menendez A, Chow KC, Pan OCC and Scott JK. 2004. Human Immunodeficiency Virus Type 1-Neutralizing Monoclonal Antibody 2F5 is Multispecific for Sequences Flanking the DKW Core Epitope. *J Mol Biol.* 338:311-327.

Menendez A, Calarese D, Stanfield RL, Chow KC, Scanlon C, Kunert R, Katinger H, Burton DR, Wilson IA and Scott JK. 2008. A Peptide Inhibitor of HIV-1 Neutralizing Antibody 2G12 Is Not a Structural Mimic of the Natural Carbohydrate Epitope on gp120. *FASEB J.*, in press.

Saphire EO, Montero M, Menendez A, van Houten E, Pantophlet R, Zwick MB, Parren PW, Burton DR, Scott JK and Wilson IA. 2007. Crystal Structure of a Broadly Neutralizing Anti-HIV-1 Antibody in Complex with a Peptide: Mechanism of gp120 Cross-reactivity. *J Mol Biol.* 369:696-709.

Jamie Scott
continued

Immunogenicity of the membrane-proximal external region of HIV-1 gp41 (MPER)

Need: Three of the 6 broadly neutralizing monoclonal antibodies against HIV-1 bind the MPER. Very likely, this region is structured by the viral membrane, and the membrane may form part of the epitopes for these monoclonal antibodies. As broadly neutralizing antibodies hold promise for protecting against HIV infection, the MPER is a logical and potentially important target for HIV vaccine design.

Goal: To prepare a DNA vaccine that produces the MPER in the context of the cell membrane, and to determine if the MPER in this context is antigenic (binds neutralizing antibodies against the MPER) and is immunogenic (elicits MPER cross reactive antibodies), and if so, if those antibodies are neutralizing.

Accomplishments: Several constructs were made tethering the MPER and various fragments of gp41 to the cell surface via either the transmembrane region from gp41 (gp41-TM) or from the platelet derived growth factor receptor (PDGFR-TM). Both bound monoclonal antibodies 2F5 the same, whereas MPER tethered to the gp41-TM bound monoclonal antibodies 4E10 better than MPER tethered to the PDGFR-TM, indicating that the TM region can affect the structure of the MPER and accessibility to neutralizing antibodies. We showed that the MPER can be immunogenic, but that it does not elicit strong enough antibody responses to neutralize virus. Boosting DNA primed animals with VLPs carrying the MPER did not boost MPER activity.

Jamie Scott
continued

Impact: We showed DNA vaccines can elicit anti-MPER antibodies, however, their titres were low. Titres must be raised by adjuvants before it can be determined whether the MPER in the context of the viral or cell membrane can elicit neutralizing antibodies.

Publications:

PhD dissertation of M. Montero. Immunogenicity of the Membrane-Proximal External Region of HIV-1 gp41 Protein as a DNA Vaccine. US provisional patent filed on behalf of SFU, 26 March 2007.

The burden of rotavirus-associated gastroenteritis in young Canadian children

Need: The recent availability of rotavirus vaccines introduces the need for a current assessment of the burden of rotavirus-associated gastroenteritis in order to facilitate recommendations and decision making regarding rotavirus vaccination.

Goal: We used a cohort model to synthesize information coming from various sources and focus on describing and quantifying the epidemiological and economic burden of community-acquired rotavirus infections in Canada.

Accomplishments: We estimated the annual number of community-acquired rotavirus-associated gastroenteritis in Canadian children aged less than 5 years, related healthcare resource utilization (physician consultations, emergency room visits and hospitalizations) and costs (direct costs to health care system, parental work loss and out-of-pocket expenses).

Impact: This model can be used to estimate the benefits a rotavirus immunization program would have in Canada.

Publications:

Sénécal M, Quach C and Brisson M. 2006. The Burden of Rotavirus-Associated Gastroenteritis in young Canadian Children: a Cohort Model. Vancouver, British Columbia, Canada, Canadian Public Health Association 97th Annual Conference. 5-30-2006.

Measuring the impact of rotavirus acute gastroenteritis episodes (MIRAGE)

Need: Current assessments of the burden of rotavirus-related acute gastroenteritis are needed to evaluate rotavirus immunization interventions.

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Health economic and outcomes research manager
Merck Frosst Canada Ltd.

Supported by:
Merck Frosst Canada Ltd.

Goal: The objective was to characterize the burden of rotavirus-related acute gastroenteritis among children presenting in out-patient settings with gastroenteritis.

Accomplishments: The following aspects of the burden of rotavirus-acute gastroenteritis were described: 1) The symptoms, health-care resource utilization and work lost associated with rotavirus acute gastroenteritis. 2) The health-related quality of life lost by children and parents because of rotavirus acute gastroenteritis. 3) The rotavirus genotype/strains associated with medically attended gastroenteritis cases in Canada.

Impact: This study provides local and current epidemiological data describing the burden of rotavirus acute gastroenteritis.

Publications:

Sénécal M, Brisson M, Lebel MH, Yaremko J, Wong R, Gallant LA, Garfield H, Ableman D J, Ward RL, Sampalis J and Mansi JA for the MIRAGE study group. 2006. Severity, Healthcare Resource Use and Work Loss Related to Rotavirus-Associated Gastroenteritis: A Prospective Study in Community Practice. Winnipeg, Canada, 7th Canadian Immunization Conference, December 3-6, 2006.

Sénécal M, Brisson M, Lebel MH, Yaremko J, Wong R, Gallant LA, Garfield, H, Ableman DJ, Ward RL, Sampalis J and Mansi JA for the MIRAGE study group. 2006. Quality of Life Lost Associated With Rotavirus Gastroenteritis in Canadian Families: A Prospective Community-Based Study. Winnipeg, Canada, 7th Canadian Immunization Conference, December 3-6, 2006.

Sénécal M, Brisson M, Lebel MH, Yaremko J, Wong R, Gallant LA, Garfield H, Ableman DJ, Ward RL, Distephano DJ, Sampalis J and Mansi JA for the MIRAGE study group. 2006. G-Serotype Distribution of Rotavirus-Associated Gastroenteritis

in Canada: a Community-Based Study Winnipeg, Canada, 7th Canadian Immunization Conference, December 3-6, 2006. Submitted to the Canadian Journal of Infectious Disease.

Sénécal M, Brisson M, Lebel MH, Yaremko J, Wong R, Gallant LA, Garfield H, Ableman, DJ, Ward RL, Sampalis J, Brisson M and Mansi JA for the MIRAGE study group. Measuring the Impact of Rotavirus Acute Gastroenteritis Episodes (MIRAGE): A Prospective Community-Based Study.

Describing the clinical and economic burden of ano-genital warts in Quebec

Need: Quantifying the burden of ano-genital warts prior to mass immunization campaign is necessary to assess the value of preventing infections with HPV types 6 and 11. It is also essential to evaluate the impact HPV vaccination programs will have on this aspect of the burden HPV infections.

Goal: The objectives are to describe, over the past decade: 1) The prevalence and the incidence of ano-genital warts requiring medical attention in Québec. 2) The healthcare resources being used for the treatment and management of genital warts. 3) The economic burden of ano-genital warts in Québec.

Impact: This will provide a picture of the burden of ano-genital warts in Quebec prior to mass HPV immunization campaign.

Martin Sénécal
continued

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Supported by:

Primarily by the Ministries of Health in participating provinces with approximately 20% also provided by PHAC and 20% by CIHR to date. Sponsors to date have included: BC Ministry of Health, BC Immunization Subcommittee & BC Centre for Disease Control; Alberta Health and Wellness; Institut national de santé publique du Québec; Public Health Agency of CIHR.

Component-specific estimates of trivalent influenza vaccine effectiveness based on a sentinel physician network

Need: Influenza is a highly changeable virus. To keep pace with evolution in the influenza virus from year to year, a new formulation of influenza vaccine has to be reconsidered annually. Despite annual revision to the vaccine, there is currently no requirement or established system for monitoring how well the revised formulation protects each year. Through the pre-existing platform of a sentinel influenza surveillance network in several provinces, we have strategically linked sentinel physicians, regional epidemiologists, and virologists in a public health initiative to evaluate vaccine protection each year based on test-negative case-control methods.

Goal: To link new influenza variant detection with annual trivalent vaccine efficacy estimation, including component-specific cross-protection during seasons of suboptimal match for some, but not all, of the vaccine antigens.

Accomplishments: Pilot projects began during the 2004-05 season and were repeated during the 2005-06 season in British Columbia. Lessons learned helped refine methodology, with expansion to include sentinel networks in the provinces of Alberta and Quebec during the 2006-07 season and also Ontario during the 2007-08 season.

Impact: The list of persons recommended to receive publicly funded influenza vaccine has been greatly expanded in recent years, including a recommendation for universal immunization in some areas. Given rapidly evolving virus, annually changing vaccine, expanding recommendations, and substantial public health investment each year, routine monitoring of influenza vaccine efficacy is a public health obligation.

The influenza vaccine is trivalent, including representative strains of 2 influenza A subtypes (both H3N2 and H1N1) and 1 influenza B lineage (either Yamagata or Victoria). Previous randomized controlled trials conducted during select seasons to evaluate vaccine efficacy have typically reported only a single overall estimate of reduction in illness resulting from any influenza virus. However, the amount of vaccine protection varies with the specific component and the proportionate mix of circulating influenza types, subtypes, strains, and drift variants in the community. Therefore, overall vaccine efficacy estimates are not generalizable from one year to the next or to communities with a different profile of circulating viruses. We have been able to derive component-specific estimates that can then be interpreted in the context of individual community experience with circulating virus subtypes.

Early understanding of the profile of circulating viruses and variants could better inform the selection of vaccine components from year to year. Timely measurement of vaccine performance can also guide recommendations for adjunct measures related to prevention or treatment during seasons of suboptimal vaccine protection. Finally, understanding the variation in individual-level vaccine efficacy is needed to guide program changes and interpret population impacts; without this information, we cannot compare current or proposed program changes (targeted vs universal) across regions or over time.

Publications:

Skowronski DM, Gilbert M, Tweed SA, *et al.* 2005.

Effectiveness of vaccine against medical consultation due to laboratory-confirmed influenza: results from a sentinel physician pilot project in British Columbia, 2004-05. *Canada Communicable Disease Report* 31:181-192.

Skowronski DM, Masaro C, Kwindt TL, *et al.* 2007. Estimating vaccine effectiveness against laboratory-confirmed influenza using a sentinel physician network: results from the 2005-

Danuta Skowronski
continued

Supported by:

Primarily the BC Ministry of Health and the BC Centre for Disease Control.

2006 season of dual A and B vaccine mismatch in Canada. *Vaccine* 25:2842-2851.

Mak A, Rahmanian R, Lei V, Lawrence D, Krajden M, Brunham RC, Skowronski D, Li Y, Booth T, Goh SH and Petric M. 2006. Longitudinal analysis of genotype distribution of influenza A virus from 2003 to 2005. *J Clin Microbiol.* 44:3583-3588.

Skowronski DM, De Serres G, Dickinson J, Petric M, Mak A, Fonseca K, Kwindt TL, Chan T, Bastien N, Charest H and Li Y. Component-specific effectiveness of trivalent influenza vaccine measured through a sentinel physician network, 2006-07, submitted.

Directed influenza evaluation and management

Need: Substantial investment is made annually in the prevention and control of influenza.

Goal: Evaluative research, critical appraisal and synthesis of evidence are needed to guide strategic vaccine recommendations and inform public policy related to seasonal influenza and pandemic preparedness.

Accomplishments: Primary research, analysis of administrative databases and critical appraisal/systematic review of available evidence have been conducted related to: elderly antibody response to vaccine, safety and cost-effectiveness of influenza immunization among infants/toddlers, timeliness and prediction of medical visits for influenza in young children in predicting P&I hospitalization and deaths in the community, determinants of health-care worker influenza immunization, assessment of influenza immunization for healthy pregnant women etc.

Impact: More strategic, efficient, effective and cost-effective public policy around influenza prevention and control.

Publications:

Sebastian R, Skowronski DM, Chong M, Dhaliwal J and Brownstein JS. 2008. Age-related trends in the timeliness and prediction of medical visits, hospitalizations and deaths due pneumonia and influenza, British Columbia, Canada 1998-2004. *Vaccine* 26:1397-1403.

Skowronski DM, Tweed SA and De Serres G. 2008. Rapid decline of influenza vaccine-induced antibody in the elderly: is it real, or is it relevant? *J Infect Dis.* 197:490-502.

Skowronski DM, Jacobsen K, Daigneault J, Remple VP, Gagnon L, Daly P *et al.* 2006. Solicited adverse events after influenza immunization among infants, toddlers, and their household contacts. *Pediatrics* 117:1963-1971.

Skowronski DM, Woolcott JC, Tweed SA, Brunham RC and Marra F. 2006. Potential cost-effectiveness of annual influenza immunization for infants and toddlers: experience from Canada. *Vaccine* 24:4222-4232.

Pourbohloul B, Meyers LA, Skowronski DM, Krajden M, Patrick DM and Brunham RC. 2005. Modeling control strategies of respiratory pathogens. *Emerg Infect Dis.* 11:1249-1256.

Rapid evaluation, research and response capacity for the prevention and control of emerging respiratory pathogens and other public health threats

Need: Influenza is a constantly re-emerging virus and the vaccine must be updated annually in response. During the 2000-01 influenza season, oculo-respiratory syndrome emerged as an unexpected adverse event following influenza immunization, requiring rapid evaluation of vaccine safety as the immunization campaign continued to unfold across Canada. Subsequently, in 2003, SARS emerged as a public

Danuta Skowronski

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Supported by:

Primarily by provincial Ministries of Health with support also from PHAC and CIHR.

Danuta Skowronski
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health threat for which new knowledge and understanding had to be generated rapidly and for which rapid vaccine development became a priority option for consideration. In 2004, avian influenza of the H7N3 subtype in the Fraser Valley, British Columbia resulted in the largest poultry outbreak in Canadian history with need again for rapid evaluation and applied public health research related to human health implications, immunization of exposed farmers and workers, and other prevention and control measures.

Goal: To establish and rehearse innovative and sustainable rapid evaluation, research and response capacity to optimally address emerging public health threats.

Accomplishments: During several recent and rapidly evolving crises, researchers were able to partner in order to generate important new knowledge to inform public policy real-time and to simultaneously develop and rehearse capacity to respond to the next public health threat.

Impact: A broad array of rapidly conducted research by a handful of investigators across Canada supported the public policy decision to continue the influenza immunization program during the 2000-01 season. Follow-up epidemiologic, immunologic, clinical and basic science research during subsequent seasons identified possible causes of oculo-respiratory syndrome and led to manufacturing changes, identified possible immunologic mechanisms, ruled out IgE-mediated syndrome and concluded a low risk of recurrence among those who had experienced the event in 2000.

Rapid response to SARS and evaluation of SARS candidate vaccines through the SARS Accelerated Vaccine Initiative in British Columbia and partnering agencies proved public health capacity and established this as the model for other rapid vaccine development proposals.

Rapid response to the H7N3 avian influenza outbreak in BC limited the number of human cases to two proven infections. Sero-survey and evaluation of protective measures, including vaccine, antivirals and PPE led to recommendations for further limiting human risk during future AI outbreaks.

Publications:

Skowronski DM, De Serres G, Scheifele D, Russell ML, Warrington R, Davies HD *et al.* 2003. Randomized double-blind placebo-controlled trial to assess the rate of recurrence of oculo-respiratory syndrome following influenza vaccination among persons previously affected. *Clin Infect Dis.* 37:1059-1066.

Skowronski DM, Strauss B, De Serres G, MacDonald D, Marion SA, Naus M *et al.* 2003. Oculo-respiratory syndrome: a new influenza vaccine-associated adverse event? *Clin Infect Dis.* 36:705-713.

Skowronski DM, Petric M, Daly P, Parker RA, Bryce E, Doyle PW *et al.* 2006. Coordinated response to SARS, Vancouver, Canada. *Emerg Infect Dis.* 12:155-158.

See RH, Zakhartchouk AN, Petric M, Lawrence DJ, Mok CP, Hogan RJ, Rowe T, Zitzow LA, Karunakaran KP, Hitt MM, Graham FL, Prevec L, Mahony JB, Sharon C, Auperin TC, Rini JM, Tingle AJ, Scheifele DW, Skowronski DM, Patrick DM, Voss TG, Babiuk LA, Gauldie J, Roper RL, Brunham RC and Finlay BB. 2006. Comparative evaluation of two severe acute respiratory syndrome (SARS) vaccine candidates in mice challenged with SARS coronavirus. *J Gen Virol.* 87:641-650.

Skowronski DM, Li Y, Tweed SA, Tam TW, Petric M, David ST *et al.* 2007. Protective measures and human antibody response during an avian influenza H7N3 outbreak in poultry in British Columbia, Canada. *CMAJ* 176:47-53.

Danuta Skowronski
continued

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Supported by:

Merck Frosst Canada Ltd. (70%); INSPQ (30%)

HPV genotyping in archived specimens of anal cancer diagnosed during one decade in Quebec (1995-2005)

Need: The natural history of cervical cancer and its relationship with HPV infection has been intensively studied but much less is known about anal cancer. Recently, incidence rates of anal cancer have doubled or tripled in selected areas and groups. In Quebec, anal cancer incidence rate (per 100,000 persons) ranges between 0.2 – 0.5 for men and between 0.4 – 0.7 for women and is on the rise. Indeed, between 1984 and 2001, the incidence of anal squamous cell cancer has increased by 353% among men and 134% among women in the Montreal metropolitan area. In other regions of the province, the increase was 73% and 244% respectively. A better understanding of the biology and epidemiology of this disease would help us understand the reasons for such increases.

Goal: The purpose of the study is to clarify the relationships between gender, HIV status, other clinical or risk factors and type-specific HPV infection in both anal squamous type and adenocarcinomas, with state-of-the-art methodology for HPV detection, in order to better interpret the trends observed and evaluate the preventive potential. Objectives:

- Estimate the prevalence of HPV infection in anal cancer;
- Compare HPV prevalence in adenocarcinomas and squamous anal cancers;
- Estimate the prevalence of the various HPV genotypes (multiple infection) in adenocarcinomas and squamous anal cancers;
- Examine other risk factors like HIV status, sex, age and comorbidity in their interaction with HPV status.

Accomplishments: This study provides a better understand of the biology, behaviour and recent trends of anal cancer, using state-of-the-art HPV detection techniques.

Impact: These data will clarify current trends in increase of possibly preventable HPV-related disease. When all specimens are tested, we expect to be able to detect HPV DNA in over 95% of specimens with a pathology result of high-grade lesion or worse. We will then be able to describe, for the first time, the distribution of HPV types in both anal squamous and adenocarcinomas.

Publications:

Steben M, Duarte-Franco E, Goggin P, Sampalis J, Coutlee F, Hadjeres R, Louchini R, Rodier C, Ghorbel M and Fournier B. HPV genotyping in archived specimens of anal cancer diagnosed during one decade in Quebec (1995-2005). 24th International papillomavirus conference, Beijing, China. November 3-9, 2006. (Poster)

The VIN-MONIQ study: Vulvar intraepithelial neoplasia monitoring in Quebec: Cancer and precursor lesions surveillance, clinical epidemiology, biomarkers and quality of life issues

Need: The fight against cervical cancer has relied in the past on the detection and treatment of cancer precursors, but there were no specific surveillance or preventive measures for the other cancers, which are usually detected clinically. The arrival of prophylactic HPV vaccines has brought new perspectives to reduce considerably the burden of HPV-related disease. Monitoring the impact of HPV vaccination will be particularly challenging, because of the long delay between HPV acquisition and cancer development, several years or decades later. It will require more sensitive indicators than cancer incidence to monitor the impact of vaccination strategies, particularly if the vaccine is given in young populations. Of particular interest as intermediate indicators are precursor states of these cancers, such as cervical intraepithelial neoplasia (CIN), but also of the other ano-genital cancers (AIN, VIN, VAIN or PIN).

Marc Steben and Eliane Duarte-Franco
continued

Supported by:

An application to PHAC has been submitted; an application for funding of an operational grant is planned for the winter 2009. A pilot project has been funded by Merck Frosst Canada Ltd. (80%) for the evaluation of feasibility.

Marc Steben and Eliane Duarte-Franco
continued

Goal: Develop a comprehensive approach to support the surveillance, prevention and treatment of vulvar and vaginal cancer in the province of Quebec. General objectives:

- Monitor the incidence of vulvar and vaginal cancer and its precursor lesions in the province of Quebec: estimate the incidence of vulvar and vaginal cancer precursors in Quebec by combining clinical and pathological information and evaluate the feasibility of establishing a province-wide registry for all cases of vulvar and vaginal cancers precursors for future monitoring studies;
- Clinical course: describe the natural history of vulvar and vaginal cancer and its precursors and identify current therapeutic procedures in use and their efficacy: (a) clarify the epidemiology of these diseases by analyzing their risk factors, natural history, relationship with HPV infection, anal and/or cervical lesions; (b) establish a cohort group in order to monitor the evolution of these conditions and support the development of evidence-based treatment;
- Monitor and standardize laboratory approaches; study known and novel biomarkers: validate laboratory tools to identify and standardize the diagnosis of vulvar and vaginal cancer precursors by using pathology, virology and molecular biology approaches; and
- Study quality of life, psychological, sexual and social issues related to the diagnosis and treatment of vulvar and vaginal cancers and their precursors

Accomplishments: The proposition of this study has never been attempted; VIN-MONIQ will be the first longitudinal study to quantify burden of disease, in particular, mental and sexual health, document trends over time, and help evaluate the potential for relief of significant suffering through primary prevention of the HPV-associated ano-genital disease.

Impact: Of all non-cervical sites, vulvar cancer and its precursors (VIN2/3) are of particular interest for several reasons:

- The incidence of vulvar cancer is relatively high, compared to the other ano-genital sites; in 1999-2001, it was established at 1.3 per 100,000 in the Quebec population;
- Research and clinical data have shown that vulvar cancer precursors are much more frequent than vulvar cancers and may contribute significantly to the burden of disease;
- Although vulvar cancer incidence appears relatively stable in most places including Quebec, the VIN incidence has been reported to be rising in several places, and tends to affect populations at a younger age, suggesting changes in risk factor prevalence;
- Vulvar cancer is a heterogeneous disease and its natural history is not fully understood; in general, it has been estimated that 40 to 50% are caused by HPV, but this proportion is higher among young women and in VIN; HPV 16 seems to be the predominant type;
- The optimal management of VIN is not clearly defined (observation, excision, use of topical immunomodulators) and may vary by clinicians and institutions. Follow-up data is necessary to support evidence-based guidelines;
- Vulvar cancer and vulvar precursors can have a major impact on the quality of life of affected women, and the treatment can be quite mutilating; yet, very little research has been carried out to evaluate the phenomenon and guide psychological, social and sexual intervention;
- Unlike cervical cancer screening and follow-up of abnormalities, the use of HPV tests and molecular markers has not been integrated in algorithms and their role needs to be defined;
- Synchronous or metachronous neoplasia of the ano-genital tract have been observed, but more data is needed, particularly by prospective studies to understand the natural history of these lesions in relation to HPV infection and define the best surveillance measures for women affected with a first vulvar intraepithelial lesion; and
- Although primary vaginal cancers are less common than vulvar cancer, they may share common characteristics, and be diagnosed and followed at the same facilities in Quebec.

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continued

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Supported by:
NSERC, SHRF, ALIDF,
Sask ADF

Non human adenoviruses as vaccine vectors

Need: *Animal Vaccination:* Although immunization has a great impact on the economics of livestock production and on animal suffering, today's vaccines produced by conventional means are imperfect in many respects including virulence, safety and efficacy. Thus, there is a need for developing safe and cost-effective vaccines. We have chosen to develop animal adenovirus-based vaccines for cattle [bovine adenovirus (BAdV)-3 based vectored vaccines] and pigs [porcine adenovirus (PAdV)-3 vectored vaccines]. The development and use of vaccines based on BAdV-3/PAdV-3 vector systems will be cost effective (a requirement for veterinary vaccines), safe with no risk of producing disease. In addition, these vaccines can also be used for eradication programs since infected and vaccinated animals can be differentiated. *Human vaccination:* Human adenoviral vectors have shown great promise and some success in clinical trials of vaccination/gene therapy. However, pre-existing viral immunity and toxicity has limited the use of HAdVs as a vaccine delivery vector. The advantageous properties of (BAdV-3; PAdV-3) including species specificity (thus providing safety against inappropriate vector replication), human cell transduction without replication, absence of pre-existing immune response in humans, and absence of packaging by HAdV in natural infection makes them attractive candidates for delivering vaccine antigens to humans. Hence, we are currently evaluating the potential of developing and using BAdV-3/PAdV-3 as vectors for human vaccination.

Goal: Our goal is to develop and use BAdV-3/PAdV-3 vectors to produce a new generation of safe, cost-effective, and highly efficacious vaccines for animals and humans.

Accomplishments: We have carried out molecular characterization of BAdV-3/PAdV-3 and have developed replication-competent and replication-defective BAdV-3/PAdV-

3 based vectors. Moreover, we have developed, tested and confirmed the feasibility of using BAdV-3/PAdV-3 as live viral vectors for delivery of vaccine antigens to the mucosal surfaces of cattle/pigs. Currently, we are evaluating the feasibility of using BAdV-3/PAdV-3 as vectors for human vaccination and developing BAdV-3/PAdV-3 vectors targeted to appropriate cells of the immune system.

Impact: Development and availability of vaccine delivery platform technology based on non-human adenovirus vectors will help to develop cost-effective, safe and efficacious vaccines for animals and humans. A number of patents protecting the intellectual property have already been awarded.

Publications:

Zakhartchouk AN, Connors W and Tikoo SK. 2004. Bovine adenovirus type 3 containing heterologous protein in the C-terminus of minor capsid protein pIX. *Virology* 320:291-300.

Wu Q and Tikoo SK. 2004. Altered tropism of bovine adenovirus 3 expressing chimeric fiber. *Virus Res.* 99:11-17.

Zakhartchouk A N, Zhou Y and Tikoo SK. 2003. A recombinant E1 deleted porcine adenovirus-3 as an expression vector. *Virology* 313:377-383.

Hammond JM, Jansen ES, Morrissy CJ, van der Heide B, Goff WV, Williamson MM, Hoover P, Babiuk LA, Tikoo SK and Johnson MA. 2001. Vaccination of pigs with a recombinant porcine adenovirus expressing the gD gene of pseudorabies virus. *Vaccine* 19:3752-3758.

Zakhartchouk AN, Pyne C, Mutwiri G, Papp Z, Baca-Estrada ME, Griebel P, Babiuk LA and Tikoo SK. 1999. Mucosal immunization of calves with recombinant bovine adenovirus-3: Induction of protective immunity to bovine herpesvirus-1. *J Gen Virol.* 80:1263-1269.

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continued

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Supported by:

CIHR (50%), Krembil
Foundation (50%)

Respiratory syncytial virus (RSV) pathogenesis and vaccine development

Need: Although identified as the major cause of viral lower respiratory infection in humans, and particularly severe in very young infants, no RSV vaccine is available. This is in part due to the need to induce balanced immune responses, which is a challenge as neonates have difficulty mounting a robust cell-mediated immune response.

Goal: The overall objective is to investigate pathogenesis of RSV, in particular the effects on dendritic cells, and develop a rational approach to vaccine development for the newborn. An effective vaccine should be safe, and induce a balanced immune response in the newborn even in the presence of maternal antibodies.

Accomplishments: Novel formulations for RSV vaccines were developed based on combining immunomodulatory compounds with particulate systems for mucosal delivery. These formulations could balance the immune response induced in mouse and newborn calf models, as well as elicit protection.

Impact: The novel formulations were first tested with a killed inactivated vaccine. To address potential safety concerns about a whole virus preparation, this approach will now be further evaluated with a recombinant RSV fusion protein.

Publications:

Mapletoft JW, Oumouna M, Kovacs-Nolan J, Latimer L, Mutwiri G, Babiuk LA and van Drunen Littel-van den Hurk S. 2008. Intranasal immunization of mice with a formalin-inactivated bovine respiratory syncytial virus vaccine co-formulated with CpG oligodeoxynucleotides and polyphosphazenes results in enhanced protection. *J Gen Virol.* 89:250-260.

Mapletoft JW, Oumouna M, Townsend HG, Babiuk LA and van Drunen Littel-van den Hurk S. 2006. Formulation with CpG oligodeoxynucleotides increases cellular immunity induced by vaccination of calves with formalin-inactivated bovine respiratory syncytial virus. *Virology* 353:316-323.

Oumouna M, Mapletoft JW, Karvonen BC, Babiuk LA and van Drunen Littel-van den Hurk S. 2005. Formulation with CpG oligodeoxynucleotides prevents induction of pulmonary immunopathology following priming with formalin-inactivated or commercial killed bovine respiratory syncytial virus vaccine. *J Virol.* 79:2024-2032.

Characterization of dendritic cell - hepatitis C virus (HCV) interactions and relevance for hepatitis C therapy

Need: An estimated 170 million people are currently infected with HCV worldwide, which amounts to 1-3% of the world population and is higher than the number of HIV patients. According to a 2004 report, hepatitis C occurs at a rate of 44.7 per 100,000 in Canada. Treatment is not always effective, is costly and is accompanied by serious side effects.

Goal: The overall objective is to develop dendritic cell-based vaccination strategies for hepatitis C.

Accomplishments: Vaccination of mice with HCV NS3/4a or NS5a protein-pulsed or mRNA-transfected dendritic cells resulted in significant CD4⁺ and CD8⁺ T cell responses and protection from challenge with vaccinia virus expressing NS3/NS4/NS5. These results are promising, but need to be expanded to human dendritic cells.

Impact: Since dendritic cell maturation and function are modulated by the microenvironment, which may be different and not optimal in chronic HCV patients *in vivo* in comparison to healthy humans, we expect dendritic cell therapy to be

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continued

effective against chronic hepatitis C. Dendritic cell therapy would circumvent the diminished and down-regulated dendritic cell function of these patients *in vivo* by giving necessary maturation stimuli *ex vivo*.

Publications:

Yu H, Babiuk LA and van Drunen Littel-van den Hurk S. 2008. Strategies for loading dendritic cells with hepatitis C NS5a antigen and inducing protective immunity. J Viral Hepatitis, in press.

Needle-free vaccines for respiratory viruses

Need: Respiratory viruses are one of the main causes of mortality from infectious diseases in the developing world and cause considerable morbidity in industrialized countries. The available vaccines have to be injected, which causes logistical problems and risk of cross-contamination in the developing world, and is a frequent reason for non-compliance in industrialized countries.

Goal: The goal of the project is to formulate vaccines for intranasal inoculation and assess their efficacy in appropriate animal models.

Accomplishments: Our group developed virus purification and vaccine formulation protocols for canine distemper virus as a model for measles virus. The efficacy studies are currently under way.

Impact: We expect that the efficacy assessment in the highly sensitive ferret model will demonstrate the value and safety of this new vaccination approach and contribute to its accreditation and ultimately widespread use.

Publications:

Our work is still ongoing, but Dr. Brian Ward, the principal investigator of this project, has published other aspects of the work in:

Chabot S, Brewer A, Lowell G, Plante M, Cyr S, Burt DS and Ward BJ. 2005. A novel intranasal Protollin-based measles vaccine induces mucosal and systemic neutralizing antibody responses and cell-mediated immunity in mice. *Vaccine* 23:1374-83.

Pasetti MF, Resendiz-Albor A, Ramirez K, Stout R, Papania M, Adams RJ, Polack FP, Ward BJ, Burt D, Chabot S, Ulmer J,

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Supported by:

CIHR University-Industry Grant

Veronika von Messling
continued

Supported by:
Mostly internal funds

Barry EM and Levine MM. 2007. Heterologous prime-boost strategy to immunize very young infants against measles: pre-clinical studies in rhesus macaques. *Clin Pharmacol Ther.* 82:672-685.

Cyr SL, Jones T, Stoica-Popescu I, Brewer A, Chabot S, Lussier M, Burt D and Ward BJ. 2007. Intranasal proteosome-based respiratory syncytial virus (RSV) vaccines protect BALB/c mice against challenge without eosinophilia or enhanced pathology. *Vaccine* 25:5378-5389

Efficacy assessment of available pandemic influenza vaccines

Need: Several pandemic (H5N1) influenza vaccines have been developed and are now commercially available in different parts of the world, but their efficacy has never been evaluated side-by-side. In the case of a pandemic, it will be essential to know the potential and limitations of each product.

Goal: To assess the efficacy of commercially available H5N1 vaccines in different animal models.

Accomplishments: This is a collaborative project with Dr. Heinz Feldmann and others at the National Microbiology Laboratory in Winnipeg. The project started in 2007, and a CIHR team grant application has been submitted in January 2008. Our first study showed that adenoviral vectors expressing the HA of H1N1 1918 elicit a stronger humoral and cellular immune response than the conventional split vaccine in ferrets and protect them better from subsequent challenge.

Impact: We expect that the results will help policy makers to react appropriately in the case of a pandemic, and that the data produced will lead to the development of more efficient influenza vaccines.

Pan-specific cellular immune response to influenza

Need: The currently available vaccines for influenza provide little protection against other subtypes. New vaccine approaches are needed to elicit a pan-specific response that provides protection against newly emerging subtypes.

Goal: To evaluate the vaccine efficacy of a highly conserved influenza T cell epitope.

Accomplishments: The study has only started in 2007, and the expression constructs are still being generated in the laboratory of the principal investigator of this study, Dr. Rejean Lapointe. Dr. Lapointe has shown *in vitro* that the vaccine is recognized by T cells from human volunteers that had been vaccinated, and the first series of systematic mouse studies will start in spring.

Impact: We expect that this vaccine approach, possibly in combination with the conventional vaccine, will increase its efficacy against other subtypes.

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continued

Supported by:
CIHR Pandemic Preparedness
Strategic Research Initiative
operating grant

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Supported by:
CIHR/RPP

Understanding tissue microenvironment and regulatory mechanisms of induction and maintenance of mucosal immunity

Need: An effective vaccine is the one that is able to induce long-lasting protective humoral and/or cellular immunity. Since most of the infectious diseases affecting world populations such as tuberculosis, HIV, influenza, or gastrointestinal infectious diseases are acquired via the mucosal route, mucosal vaccination is proposed as an optimal strategy to prevent infectious diseases. While the cellular immune response is required to fight intracellular pathogens such as viruses, some bacteria and parasites, cellular immunity also causes inflammation that can compromise the function of mucosal tissues when not controlled optimally. Therefore, the challenge in mucosal vaccine development is to induce an optimal response without compromising tissue function. A comprehensive understanding of immune mechanisms that control the induction and maintenance of long-term protective immunity in mucosa is essential for developing effective and safe mucosal vaccines.

Accomplishments: Using recombinant replication-deficient adenovirus-based vaccines as model vaccines, we have demonstrated that the quantity and quality of memory T cells induced by intranasal immunization differ significantly from the ones induced by parenteral immunization and these differences result in different levels of immune protection against pulmonary intracellular bacterial infection. We are currently investigating how the specific mucosal tissue microenvironment contributing to these differences and through which regulatory mechanisms.

Impact: Our results highlight the importance of intranasal vaccination against airborne intracellular pathogens. Understanding of underlying mechanisms will have significant impact in the design of effective and safe mucosal vaccines.

Publications:

Wang J, Thorson L, Stokes RW, Santosuosso M, Huygen K, Zganiacz A, Hitt M and Xing Z. 2004. Single mucosal, but not parenteral, immunization with recombinant adenoviral-based vaccine provides potent protection from pulmonary tuberculosis. *J Immunol.* 173:6357-6365.

Santosuosso M, Zhang X, McCormick S, Wang J, Hitt M and Xing Z. 2005. Mechanisms of mucosal and parenteral tuberculosis vaccinations: adenoviral-based mucosal immunization preferentially elicits sustained accumulation of immune protective CD4 and CD8 T cells within the airway lumen. *J Immunol.* 174:7986-7994.

Wang J and Xing Z. 2002. Tuberculosis vaccines: the past, present and future. *Exp Rev Vaccines* 1:341-354.

Development of effective and safe mucosal vaccines against *Chlamydia* species based on recombinant gene delivery systems

Need: Intracellular bacteria *Chlamydia trachomatis* and *Chlamydia pneumoniae* enter the human body through multiple mucosal sites causing a wide spectrum of ocular, genital and respiratory diseases of significant medical importance worldwide. Although antibiotics are effective for the treatment of acute chlamydial infections, asymptomatic infections are rampant, often making clinical presentations of complications the first evidence of an infection. A safe and effective *Chlamydia* vaccine that can prevent chlamydial infections is urgently needed.

Accomplishments: We are exploring multiple recombinant gene delivery vectors for mucosal delivery. Recently, we have successfully constructed a recombinant adenovirus-based *Chlamydia* vaccine expressing chlamydial protease-like activity factor (AdCPAF). Preliminary studies indicated that AdCPAF

Jun Wang

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NSHR Health Project

Jun Wang
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stimulated both humoral and cellular immunity in mice. Intranasal immunization with AdCPAF provided immune protection in the lung and female genital tract.

Impact: A safe and effective *Chlamydia* vaccine will provide significant social and economic benefits to the world.

Publications:

David J, Moore JM, Zhong G, Xing Z, Lee SF, Halperin SA and Wang J. 2008. Construction and characterization of recombinant adenovirus-based *Chlamydia* vaccine. Poster presentation at Canadian Society of Immunology 21st Annual Meeting, Quebec, Canada, April 2008 (Poster #126).

Development of inactivated, nasal vaccines for respiratory viruses such as measles, RSV and human parainfluenza virus type 3 (PIV3)

Need: Vaccines for several of the most important respiratory viruses do not currently exist (e.g.: RSV, PIV3). The development of these products has been complicated by poorly-understood, aberrant responses to early candidate vaccines. Good vaccines already exist for several other respiratory viruses (e.g.: measles, mumps, rubella) but are associated with rare adverse events. As these diseases are targeted for eradication, new and safer vaccines will be needed to maintain high vaccine coverage rates.

Goal: We proposed to exploit new vaccine delivery and adjuvant systems (proteosomes and Protollin) to develop a series of candidate split-virion vaccines for nasal administration. We further proposed to study the immunologic mechanisms associated with the aberrant lung responses.

Accomplishments: We have successfully produced novel vaccines that are safe and immunogenic in mice. These candidate vaccines elicit local and systemic immune responses that would be predicted to be protective *in vitro* (i.e. neutralizing antibodies) or have demonstrated protection directly in animal models. Our candidate measles vaccine has been tested in a limited number of primates and found to be effective. The molecular mechanisms that underlie the adjuvant effects have been dissected using knock-out animals. This novel adjuvant-delivery system was found to completely abrogate the aberrant respiratory response reported for RSV. Finally, we have demonstrated that several of our split-virion antigens can be combined (measles-PIV3, measles-mumps to date) without loss of immunogenicity.

Impact: Our candidate measles vaccine has been submitted for patent (under review), and we hope that further work will permit other patents to be submitted for combined vaccines (e.g. an inactivated MMR).

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Supported by:
CIHR-Industry (90%), Bill
and Melinda Gates
Foundation (10% through Dr
M Levine, U Maryland)

Brian J Ward

continued

Publications:

Rodeheffer C, Chabot S, Brewer A, Burt D and Ward BJ. Intranasal, proteosome-formulated measles vaccine is safe and immunogenic in mice and induces humoral immunity in a TLR-dependent manner, submitted.

Cyr SL, Angers I, Stoica-Popescu I, Lussier M, Qureshi S, Burt D and Ward BJ. Intranasal, Protollin-based RSV vaccination in mice: TLR4/MyD88 signaling is required both for protection and the control of pulmonary granulocyte recruitment following challenge. *J Immunol*, in revision.

Pasetti M, Resendiz-Albor A, Ramirez K, Stout R, Papania M, Adams R, Ploack F, Ward BJ, Burt D, Chabot S, Ulmer J, Barry E and Levine M. 2007. Heterologous prime boost strategy to immunize very young infants against measles. *Clin Pharmacol & Therapeutics* 82:672-685.

Cyr SL, Jones T, Stoica-Popescu I, Brewer A, Chabot S, Burt D and Ward BJ. 2007. Intranasal Proteosome-based respiratory syncytial virus (RSV) vaccines protect BALB/c mice against challenge without eosinophilia or enhanced pathology. *Vaccine* 25:5378-5389.

Chabot S, Brewer A, Plante M, Torossian K, Burt DS and Ward BJ. 2005. A novel intranasal Protollin™-based measles vaccine induces mucosal and systemic neutralizing antibody responses and cell-mediated immunity in mice *Vaccine* 23:1374-83

Supported by:

NIH (35%), IDRC (35%),
US HHS (10%), CCFC (20%)

Responding to vaccine safety concerns

Need: Many are losing confidence in vaccines. The mainstream scientific community needs to be able to respond to issues of vaccine safety in a timely fashion.

Goal: Several projects have been carried out under this general 'banner' with support from NIH, US Department of Health & Human Services, IDRC and CCFC.

Accomplishments: 1) Demonstrated that the apparent ill effects of high titre measles vaccine did not include morbidity in Sudan. 2) Documented the (relative) safety of anthrax vaccine for military personnel and 3) Contributed significantly to refuting the MMR-autism hypothesis.

Impact: See need.

Publications:

D'Souza Y, Seidman E and Ward BJ. 2007. Failure to demonstrate persistent measles virus in bowel biopsies from subjects with inflammatory bowel disease. *Gut* 56:886-888.

D'Souza Y, Fombonne E and Ward BJ. 2006. No evidence of persistent measles virus in peripheral blood mononuclear cells from subjects with autistic spectrum disorder. *Pediatrics* 118:1664-1675.

Sever JL, Brenner A, Gayle AD, Lyle JM, Moulton LH, Ward BJ and West DJ. 2004. Safety of anthrax vaccine: An expanded review of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiol Drug Safety* 13:825-840.

Libman MD, Ibrahim SA, Omer MI, Adlan IA, Bellavance F, Hoskins E, Bertley F and Ward BJ. 2002. No evidence for short or long term morbidity after increased titer measles vaccination in Sudan. *Pediatr Infect Dis J.* 21:112-119.

Leon MH, Ward BJ, Kanashiro R, Hernandez H, Vaisberg AJ, Escamilla J, Berry S and Halsey N. 1993. Changes in immune cell function and phenotype two years after high titer measles vaccination. *J Infect Dis.* 168:1097-1104.

Brian J Ward
continued

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Supported by:
CIHR

Cellular immune response to post-translationally modified peptide antigens

Need: Central immunological tolerance normally represents an important natural safeguard against the development of autoimmune disease. By the same token, immunological tolerance comprises a significant barrier to many cancer immunotherapy approaches. By identifying new antigens that can avoid central tolerance, we can potentially gain insights into both the process of autoimmune disease and novel approaches for cancer immunotherapy.

Goal: The goal of this project was to use well-characterized MHC class I and II model epitope systems to formally demonstrate that CD4 and CD8 T cells have the capacity to specifically recognize antigens containing the inflammation-associated post-translational modification 3-nitrotyrosine. This oxidative modification is routinely used as a surrogate marker of *in vitro* inflammation and has been commonly observed to be present at high levels in both autoimmune disease and cancer settings, making it an attractive target for clinical intervention.

Accomplishments: Using model systems, we have definitively proven that both CD4 and CD8 T cells are capable of recognizing peptides containing a tyrosine to nitrotyrosine conversion.

Impact: The results of our studies reveal for the first time that the inflammation-associated amino acid analogue 3-nitrotyrosine can be specifically recognized by both CD4 and CD8 T cells. Despite an intensive worldwide effort to identify antigens that constitute auto-antigens during autoimmune disease, there has been little success. Our results provide an impetus for exploring the possibility that proteins containing post-translational modifications such as 3-nitrotyrosine represent rationale and potential targets of the immune system

during autoimmune disease by evading the process of central immunological tolerance. Likewise, putative tumour antigens containing a tyrosine to nitrotyrosine conversion may represent important and innovative new targets for cancer immunotherapy.

Publications:

Birnboim HC, Lemay AM, Lam DK, Goldstein R and Webb JR. 2003. Cutting edge: MHC class II-restricted peptides containing the inflammation-associated marker 3-nitrotyrosine evade central tolerance and elicit a robust cell-mediated immune response. *J Immunol.* 171:528-532.

Hardy LL, Wick DA and Webb JR. 2008. Conversion of tyrosine to the inflammation-associated analogue 3-nitrotyrosine at either TCR-contact or MHC-contact positions can profoundly affect recognition of the MHC class I-restricted epitope of LCMV glycoprotein (gp33) by CD8 T cells. *J Immunol.*, in press.

Therapeutic vaccines for cervical cancer and pre-cancerous, cervical intraepithelial neoplasia (CIN)

Need: The recently introduced prophylactic vaccines against cervical cancer caused by infection with HPV are predicted to have a major impact on cervical cancer in the future. However, these vaccines have been shown to be effective only if administered prior to infection (HPV is an endemic viral infection and the majority of the population currently becomes infected by their second or third sexual encounter). Thus the vaccine is destined to be administered to pre-adolescent females (prior to first sexual encounter). Most of the current adult population has therefore already been exposed to virus, and the new vaccines will offer no clinical benefit, thus HPV-associated cervical cancer and CIN will continue to occur for the foreseeable future.

John R Webb
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Supported by:
Private sector

John R Webb
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Goal: The goal of this project is to generate an HPV vaccine that will confer therapeutic efficacy for those with cervical cancer or pre-cancerous, cervical intraepithelial neoplasia.

Accomplishments: We have identified a vaccine/adjuvant combination that elicits robust MHC class I-restricted CD8 T cell immunity against the E7 oncoprotein of HPV. This reagent is currently in Phase I clinical trials with a private sector company.

Impact: The current vaccine (in clinical trials with a private sector company) represents a first generation clinical product. However, we have since developed an improved product with a much broader potential scope (the first generation vaccine protects against only HPV strain 16, whereas our second generation vaccine is predicted to provide protective immunity against HPV 16 as well as four other high-risk strains of HPV).

Publications:

Wick DA, Boyle J, Rowse GJ, Emtage PC and Webb JR. 2008. Repeated Daily Immunization with the HPV therapeutic vaccine candidate HspE7 plus the TLR3 agonist poly-ICLC results in massive expansion of an E7-specific CD8⁺ T cell population and regression of large, established E7-expressing TC-1 tumors, in preparation.

Development and evaluation of novel recombinant virus-based tuberculosis vaccines in small and large animal models and human trials

Need: BCG vaccine has been used for more than 85 years in human immunization program against pulmonary tuberculosis (TB) but it has failed to effectively control adult tuberculosis, hence the current TB epidemic. One important reason for such failure is that its protective efficacy can last only for 10-15 years. Thus, there is a need to develop vaccines that are different from BCG but can be used to boost and sustain BCG-mediated protection.

Goal: Our project aims to develop novel TB vaccines that are not mycobacterial organism-based (heterologous vaccines) and can effectively boost protective T cell responses following BCG prime immunization.

Accomplishments: We have developed 2-3 recombinant adenovirus- or vesicular stomatitis virus-based TB vaccines. Some of these virus-based TB vaccines were engineered to co-express two immunodominant *M.tb* antigens (bivalent fusion protein vaccine). These vaccines have been evaluated for their immunogenicity and protective efficacy in murine models following intramuscular or intranasal route of immunization. While both routes of immunization were effective in activating antigen-specific T cells, only intranasal immunization could provide robust immune protection from pulmonary TB. Of importance, virus TB vaccines could markedly enhance immune protection triggered paracutaneous BCG vaccination. By using such virus-based TB vaccines, we have investigated the usefulness of genetic-engineered dendritic cell-based TB vaccines in murine models. Via our collaboration with the scientists at Veterinary Laboratories Agency in UK, an adenovirus-based TB vaccine has also shown promise in enhancing protective T cell responses in BCG-primed calves. With support from NIH (USA) and collaboration with scientists

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Supported by:
Sequella Global Tuberculosis Vaccine Foundation (5%), World Health Organization (10%), Canadian Foundation for Innovation & Ontario Innovation Trust (for Level III TB facility infrastructure) and CIHR (85%). An NIH contract (Texas A&M University) supported the evaluation of our recombinant adenovirus TB vaccine in guinea pig models.

Zhou Xing
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at Texas A&M University, an adenovirus-based TB vaccine was also evaluated in guinea pig models and shown to markedly prolong the survival of infected guinea pigs following BCG prime immunization.

Impact: We were the first to have reported the use of adenovirus TB vaccines. These developments in small and large animal models form a good foundation for us to forge a Phase I clinical trial to evaluate both the safety and immunogenicity of the adenovirus TB vaccine in healthy human volunteers.

Publications:

Wang J, Santosuosso M, Ngai P, Zganiacz A and Xing Z. 2004. Activation of CD8 T cells by mycobacterial vaccination protects against pulmonary tuberculosis in the absence of CD4 T cells. *J Immunol.* 173:4590-4597.

Wang J, Thorson L, Stokes RW, Santosuosso M, Huygen K, Zganiacz A, Hitt M and Xing Z. 2004. Single mucosal, but not parenteral, immunization with recombinant adenoviral-based vaccine provides potent protection from pulmonary tuberculosis. *J Immunol.* 173:6357-6365.

Santosuosso M, McCormick S, Zhang X, Zganiacz A and Xing Z. 2006. Intranasal boosting with an adenovirus-vectored vaccine markedly enhances protection by parenteral BCG immunization against pulmonary tuberculosis. *Infect Immun.* 74: 4634-4643.

Vordermeier HM, Huygen K, Singh M, Hewinson RG and Xing Z. 2006. Immune responses induced in cattle by vaccination with a recombinant adenovirus expressing mycobacterial antigen 85A and BCG. *Infect Immun.* 74:1416-1418.

Roediger EK, Kugathasan K, Zhang X, Lichty BD and Xing Z. 2008. Heterologous boosting of recombinant adenoviral prime immunization with a novel vesicular stomatitis virus vectored vaccine for pulmonary tuberculosis. *Mol Ther.* 16:1161-1169.

Respiratory mucosal vaccination strategies against tuberculosis

Need: TB represents an infectious disease of respiratory mucosa. The most effective immune protection may be accomplished by immunization at the site of infection. However, the most vaccines including some of genetic based vaccines developed to date are suitable only for parenteral immunization. The issues regarding the efficacy, mechanisms and safety of respiratory mucosal immunization remain to be addressed.

Goal: Our project aims to explore the efficacy and immune mechanisms of respiratory mucosal vaccination, as compared to parenteral vaccination.

Accomplishments: We have found that respiratory mucosal immunization with BCG vaccine or recombinant virus-based vaccines are more effective than parenteral immunization in immune protection from pulmonary TB in murine models. Of importance, we have identified that the ability to elicit and retain airway luminal T cells following immunization holds the key to immune protection. Thus, in contrast to parenteral genetic immunization, respiratory mucosal immunization is particularly potent in eliciting and retaining *M.tb*-antigen-specific T cells within the airway lumen. We have further found that airway delivery of soluble *M.tb* antigens helps recruit and retain systemically activated T cells to the airway lumen following intramuscular immunization and thus represents a powerful way to restore immune protection by parenteral virus-based or plasmid DNA-based immunization.

Impact: Our findings will help the rational design of effective mucosal or parenteral TB immunization strategies and form the basis for developing future clinic trials involving intranasal immunization.

Zhou Xing
continued

Supported by:
World Health Organization
(5%), CIHR (95%)

Zhou Xing

continued

Publications:

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Influenza and the health-care workforce: Evaluation of a novel surveillance system and identifying barriers and facilitators to vaccine uptake

Need: While elderly, frail or debilitated patients experience the highest mortality from influenza annually, health-care workers (HCWs) experience among the highest attack rates. It is known that vaccinating HCWs against influenza is cost-effective in not only reducing their risk of developing influenza with its consequent morbidity and time lost from work by needed health human resources, but also of substantially reducing mortality in patients. Nonetheless, the vaccine is still underutilized by HCWs .

Goal: While many studies have pointed to fear of side effects, lack of knowledge about the possible severity of influenza, as well as vaccine accessibility as key factors in health-care workers' decisions about being vaccinated, this study aimed to delve more deeply into the organizational and individual determinants of HCW vaccination, and also to ascertain the usefulness and challenges of vaccine uptake surveillance in the health-care setting.

Accomplishments: The safety climate in the health-care worksetting was identified as an important determinant of vaccine uptake, adding a new dimension to the findings of previous research. We were able to conclude that a coercive policy in which HCWs feel that they are forced to accept what they see as an invasive procedure or feel treated as “vectors of transmission” is not productive, whereas integrating vaccination of health workers into a comprehensive workforce health program is viewed positively. We also identified that confidentiality of vaccine records is important. We concluded that without adequate numbers of properly trained occupational health professionals to provide advice, answer questions and respond promptly to concerns, while ensuring confidentiality, a surveillance system is likely to be seen more

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as a weapon against workers than a tool for decreasing transmission of disease. We therefore have taken this into account in developing policies as well as planning the implementation of an occupational health capacity-building as well as surveillance system in health-care, now being used not only in Canada but abroad.

Impact: This is one of the first studies in Canada to explore in-depth attitudes towards workplace vaccination. Our findings confirm the importance of comprehensive approaches, underlining the importance of creating a healthy workplace culture. The impact of our findings is that this research has highlighted the importance of vaccine promotion initiatives for the health-care workforce being integrated into a facility-wide health promotion campaign and be part of on-going efforts to improve the health and working conditions of health-care workers. Moreover, the impact of our work on surveillance systems indicated that use of workplace-based health surveillance should only be undertaken where confidentiality can be assured and trained occupational health professionals can oversee the program. This resulted in more emphasis on capacity-building in South Africa's attempts to protect its health-care workforce, while implementing a surveillance system.

Publications:

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Vaccine for SARS coronavirus

Need: There is a clear need for a safe and effective SARS coronavirus vaccine should an outbreak of the infection reappear in the human population.

Goal: Our objective is to develop a vaccine for SARS coronavirus.

Accomplishments: Four different SARS vaccine candidates were tested for their immunogenicity in mice, and two of them were evaluated for ability to protect against live SARS coronavirus challenge in murine and ferret model of infection.

Impact: This brings the team a step closer to clinical trials of a SARS coronavirus vaccine.

Publications:

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Influenza A virus infection activates PI3K/Akt pathway

Need: Influenza viruses continue to pose a severe threat worldwide. The major difficulty in defending against influenza virus infection is the high genetic variability of the virus. This results in the rapid generation of reassortant viruses that can escape the acquired immunity against previous virus strains or gain resistance to antiviral agents. During virus infection, virus-host interactions determine the virus life cycle and pathogenesis. One important strategy from the virus perspective is to activate cellular signaling pathways and hijack the cellular machinery to augment viral replication and propagation. Thus, cellular events that are essential for efficient virus replication and propagation might be the target for anti-influenza interventions.

Goal: The goal is to investigate how influenza A virus activates PI3K/Akt pathway and how the pathway regulates virus propagation and pathogenesis.

Accomplishments: We demonstrated that influenza viral NS1 is critical in mediating the pathway activation and the pathway is beneficial for the virus replication.

Impact: The finding led to generation of attenuated influenza viruses, which could be candidates for live vaccine.

Publications:

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Shin YK, Liu Q, Tikoo SK, Babiuk LA and Zhou Y. 2007. Effect of PI3K/Akt pathway on influenza A virus propagation. *J Gen Virol.* 88: 942-950.

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