NOVEL *alternatives to* ANTIBIOTICS

Workshop Report

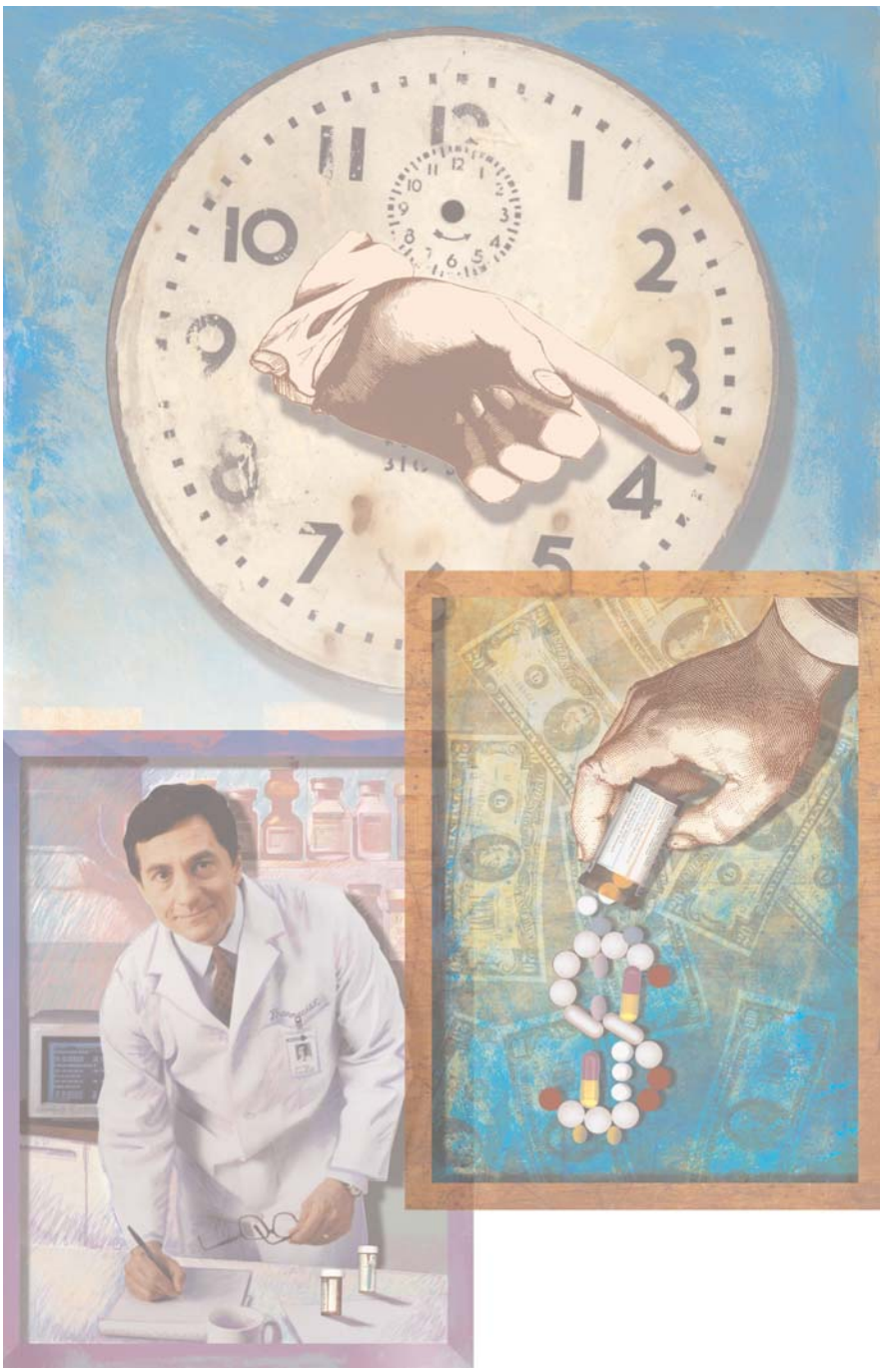
Is Time Running out for Antibiotics?

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Canada

NOVEL *alternatives to* ANTIBIOTICS

Workshop Report • March 10th and 11th, 2005 • Vancouver, British Columbia



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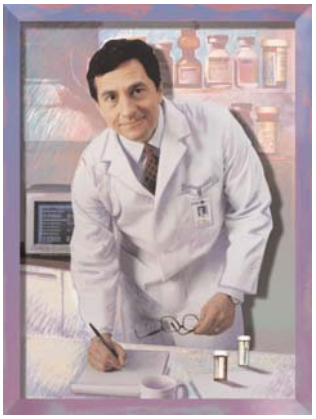
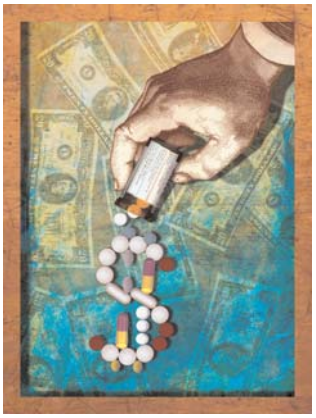


Antibiotic Resistance

Bacterial infections can strike anyone - the young, the old, the healthy and the chronically ill. Usually the body's immune system, which is designed to fight infection, defeats the invading bacteria. Sometimes however, the burden of infection proves too great, or the patient too weak perhaps because of a compromised immune system (eg. those people living with HIV/AIDS or those receiving cancer treatment). In these situations infection can be fatal. For more than 50 years, antibiotics have come to the rescue by routinely producing rapid and long-lasting 'miracle cures'. However, from the beginning antibiotics have selected for resistance in the bacterial populations that they attack - resistance than can be easily transferred between bacteria. The more an antibiotic is used, and the broader its spectrum, the more widespread resistance becomes. Because antibiotics have a rapid and long-lasting effect and are relatively inexpensive, they have sometimes been overused or misused in clinical practice, often being prescribed for infections caused by viruses, or in response to a patient's request for a 'quick fix'. In addition, the widespread use of related classes of antibiotics as growth promoters and unnecessary therapeutics in agriculture has exacerbated the problem of resistance to the antibiotics used in human health. The consequence has been a gradual rise in antibiotic resistance and the selection of bacteria that are resistant to most, if not all, available classes of antibiotics. The situation is worse in some countries than others and although Canada does not see the same high rates of resistance as the United States, antibiotic resistance is not a problem we can afford to ignore.



Antibiotic Development

Initially new drug development by the large pharmaceutical companies kept pace with rising rates of resistance, but recently the flow of new antibiotics onto the market has dramatically decreased. Increasingly, industry is turning its attention to more marketable drugs with bigger profit margins such as those used for the treatment of chronic diseases or life-style issues. We are now faced with a situation that has been compared to "a train coming down the track" - increasing drug resistance and no new drugs. There is concern that medicine could return to the pre-antibiotic days if we fail to preserve the efficacy of the antibiotics we still have, investigate new targets, screen the biologically active small molecules that exist in nature and in man-made chemical libraries, and explore novel alternatives to antibiotic use.

The Partners

Alberta Heritage Foundation for Medical Research

Association of Medical Microbiology and Infectious Disease Canada

Canadian Committee on Antibiotic Resistance

Canadian Foundation for Infectious Diseases

Community and Hospital Infection Control Association

Canadian Patient Safety Institute

Fonds de la recherche en santé du Québec

National Research Council of Canada

Public Health Agency of Canada

The above organizations were engaged in the planning and support of the workshop and will continue to work together on the development of a research agenda.

The Research Challenge

The Institute of Infection and Immunity (III) is one of the 13 virtual Institutes of the Canadian Institutes of Health Research (CIHR). Antibiotic resistance is one of the Institute's strategic research priorities. III is currently funding research on antibiotic resistance both in agriculture and human health and recently committed funds to a new CIHR health services research program to explore ways to reduce the need for antibiotics through improved infection control practices in acute and long-term health care facilities. Other health-related organizations are engaged in antibiotic resistance surveillance, epidemiology studies and educational initiatives to encourage the prudent use of antibiotics. In 2004, Dr Brett Finlay, a member of the III Institute Advisory Board, identified a need for research into novel **alternatives** to antibiotics based on the premise that not only will resistance always be generated by traditional antibiotics, but academia does not have the financial means to take new drugs to market. A small steering group was formed which, together with a number of partner organizations, identified a group of researchers known both for their research expertise and their ability to think creatively. These researchers were invited to an informal and interactive workshop entitled 'Novel Alternatives to Antibiotics', which took place in Vancouver on March 10th and 11th, 2005.

Novel Alternatives to Antibiotics Workshop

The workshop combined an overview of antibiotic resistance with free-ranging discussions on potential alternatives to antibiotics. The criteria used to identify topics included the originality of the approach, the feasibility of mounting a research initiative based on available research strengths, potential for rapid uptake of results (knowledge translation) and cost. Of the many alternatives that were suggested and discussed during the workshop several themes emerged consistently among the working groups. They were:

- *immune systems - includes immune modulation eg. promotion of innate immunity, vaccines and anti-microbial peptides*
- *microbial ecology - includes alteration of bacterial flora eg. prebiotics, probiotics*
- *bio-prospecting - includes screening of small molecules and targets*
- *phage therapy*
- *novel target identification - includes anti-virulence factors*
- *physical systems including biomaterials research*
- *rapid diagnostics - eg. 'lab on a chip'*

The Recommendations

When viewed from the perspective of responsiveness to the goals of the workshop and 'readiness' for immediate development of a research initiative, three themes emerged as being of high priority:

Immune Systems

One function of the immune response is to kill bacteria. Modulation of the host immune response, either through vaccine delivery (therapeutic and preventive) or other mechanisms to increase innate immunity, holds considerable promise as a means to fight bacterial infection. A team approach was recommended to combine the strong Canadian research expertise in immunology and microbiology.

Phage Therapy

Phage therapy was largely abandoned by the western world when antibiotics were first discovered. However phage research continued in both Poland and Russia, where antibiotic resistant infections apparently continue to be successfully treated using live phage or phage products. Recently, increasing attention has been turned towards phage therapy as a potential alternative to antibiotics. Although there is some research expertise in the Canadian agricultural and biotechnology sectors, there is little academic research capacity in Canada for phage therapy in the health sector. Despite potential regulatory problems, particularly with phage cocktails, phage therapy offers an innovative approach ideally suited to proof of concept studies. Partnership development both in Canada (with existing biotechnology companies and the agricultural sector) and inter-nationally will be key in developing a strong research agenda in this area.

Physical Systems / Biomaterials

This area of research includes modifications to the physical environment such, as hyperbaric conditions and temperature control, and the application of technologies such as lasers and UV light to reduce the risk of infection in patients undergoing treatment or surgery. The area also includes the discovery and application of biomaterials designed to reduce or eliminate bacterial growth and biofilm formation. Examples would be the introduction of 'super smooth' surfaces on artificial joints and the development of biomaterials impregnated with anti-infective agents. Most of the existing research and development in physical systems and biomaterials occurs in small biotech companies and there is currently little capacity for applied health research. However, there is enormous potential for partnership between the private sector and health sector as well as opportunities for new product development and commercialization. This was considered an excellent area for innovative partnerships between CIHR, the Natural Sciences and Engineering Research Council (NSERC) and the National Research Council of Canada (NRC).

Additional Research Areas

The other identified themes were also considered to be important research areas. It was thought that some, however, needed further development (eg. probiotics), and would benefit from an additional small focused workshop to bring together experts from the health and agriculture sectors. In other areas such as bio-prospecting and novel target identification it was recognized that the translational research required was beyond the financial means of any single organization and that collaboration between CIHR, NRC, NSERC and private industry would be highly advantageous. Rapid diagnostics is an area that underpins all antibacterial therapies including traditional antibiotics. Point-of-care diagnosis would enable more specific therapy and reduce the need for broad-spectrum antibiotics. However, this topic was not felt to be truly relevant to the mandate of the workshop and there are already many existing avenues of funding for diagnostic tool development.

Path Forward

It was recommended that a Request for Applications (RFA) be developed by III and partners for launch in 2005 and that the eligible research areas should include all the themes and topics discussed at the workshop and described in this report but with emphasis on the following three themes:

- immune systems
- phage therapy
- physical systems/ biomaterials

It was further recommended that applicants be required to clearly identify the innovative components of their research project, the contribution their results will make in reducing the problem of antibiotic resistance, expected milestones and an explanation of the process by which research findings will be translated into clinical practice. It was suggested that several different funding models should be made be available including short term programs, such as pilot projects and proof of principle studies, and longer term programs, such as small team grants, randomized control trials and operating grants. An emphasis on multidisciplinary research will be a strong component of successful applications.

III staff, the partners, and members of the III Institute Advisory Board will be guided by the recommendations in this report when making their final decision on the type of research initiative to be launched.

Resources

1. 'Bad Bugs, No Drugs' , Infectious Disease Society of America (IDSA), White Paper issued July 2004; web link: http://www.idsociety.org
2. Leeb, M. 'A Shot in the Arm.' *Nature* 2004; 431: 892-893
3. Nathan, C. 'Antibiotics at the Crossroads' *Nature* 2004; 431: 899-902
4. 'National Action Plan to Address Antibiotic Resistance' a report on a 2002 workshop organized by the Canadian Committee on Antibiotic Resistance (CCAR). Web link: http://www.ccar-ccra.com
5. Public Health Agency of Canada, Web link: http://www.phac-aspc.gc.ca/
6. Thacker, P.D. 'Set a Microbe to Kill a Microbe.' *Journal of the American Medical Association* 2003; 290: 3183-3185
7. Thiel, K. 'Old dogma, new tricks - 21st century phage therapy.' *Nature Biotechnology* 2004; 22: 31-36
8. Shnayerson, M. and Plotkin, M.J. 'The Killers Within : the deadly rise of drug - resistant bacteria.' 2002, Little, Brown and Company

WORKSHOP REPORT
(please refer to agenda in Appendix 2)

Day 1 - March 10th, 2005

Welcome and Introductions

The workshop was called to order by Dr. Judith Bray who explained the meeting logistics and informed participants that scheduled key-note speaker, Dr. Jim Hutchinson would unfortunately be unable to attend the workshop as he was stranded in St John's as a result of poor weather conditions. J. Bray introduced the Scientific Director of the CIHR Institute of Infection and Immunity (III), Dr. Bhagirath Singh, who welcomed participants and gave a brief overview of III priorities and achievements over the last five years, including funded programs in the area of antibiotic resistance.

Partnerships

J. Bray introduced representatives of the nine partner organizations supporting the goals of the workshop. Each said a few words about their organization and their interest in the topic. They were, in alphabetical order:

Organization	Representative
Alberta Heritage Foundation for Medical Research *(provided funds in support of the workshop)*	Jacques Magnan
Association of Medical Microbiology and Infectious Disease Canada	Mark Loeb
Canadian Committee on Antibiotic Resistance *(provided funds in support of the workshop)*	Rick Walter
Canadian Foundation for Infectious Diseases	Raphael Saginur
Community and Hospital Infection Control Association	Mary McNaughton
Canadian Patient Safety Institute	Joseph Gebran
Fonds de la recherche en santé du Québec	André Dascal
National Research Council of Canada	Jim Richards
Public Health Agency of Canada *(provided funds in support of the workshop)*	Mohammed Karmali

Judith Bray also introduced the other members of the Steering Committee, Brett Finlay, Marc Ouellette, Chris Bleackley and Robert Brunham [representing the CIHR Institute of Population and Public Health (IPPH)] , and the III staff who helped to organize the workshop, Erik Blache and Amanda Devost.

The first speaker was Dr. Brett Finlay
"WHY ARE WE ALL HERE?"

Highlights of the Presentation

This workshop was organized in response to the escalating problem of antibiotic resistance and the parallel decrease in antimicrobial research and development by large pharmaceutical companies. Of 89 new drugs approved in 2002, none were antibiotics and of over 400 new agents currently in development, only five are new anti-microbials, most of which are derivatives of existing drugs. Meanwhile, there are at least 12 anti-HIV drugs under development, plus five other anti-virals, five anti-parasitic drugs and three anti-fungal drugs.

There are many ways to address the problem of antibiotic resistance including enhanced education of both health care workers and the lay public, changes in prescribing practices, reduction or elimination of antibiotics as growth promoters or unnecessary therapeutics in agriculture, and improved infection control procedures. There is little doubt that more prudent use of antibiotics will extend their life and slow the progression of resistance. However, resistance will ultimately always occur either through de-novo generation or horizontal transfer and so we would be wise to consider alternatives to traditional antibiotics in the continuing battle against infectious diseases.

In 2004, the Institute Advisory Board of III made the proactive decision to tackle the problem of antibiotic resistance from the perspective of novel alternatives to antibiotics. As a first step, a steering committee was formed comprised of III IAB members (Brett Finlay, Marc Ouellette, Chris Bleackley), III staff (Judy Bray) and a representative of the IAB of the IPPH (Robert Brunham). Workshop participants selected by this steering committee, in consultation with the supporting partner organizations, were chosen not only on the basis of their successful research careers but also for their capacity to think beyond their traditional disciplines and areas of research to discuss far reaching questions about antibiotic therapeutics (see Participant List, Appendix 1). The workshop was planned to be highly interactive, with a focus on brainstorming and discussion to produce innovative ideas for novel research initiatives (See Agenda, Appendix 2). The ultimate goal of the workshop was to provide III and the partner organizations with recommendations for a joint research initiative that will capitalize on Canadian research strengths and provide alternative therapies to replace or complement the use of traditional antibiotics in medical practice.

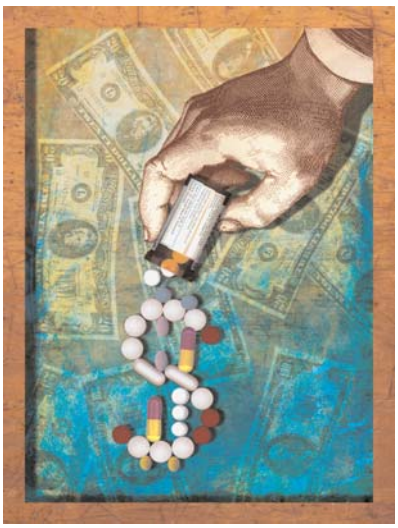
The second speaker was Dr. Julian Davies

"WHERE ARE ALL THE ANTIBIOTICS WHEN YOU REALLY NEED THEM?"

As one of Canada's leading experts in the field of antibiotic resistance, Dr. Davies was well-placed to give participants a comprehensive overview of the current situation in Canada and abroad, based on his many years of experience dating back almost to the original discovery of penicillin in the 1940's (see Dr. Davies' Biography, in Appendix 3). His talk was followed by a lively question and answer period that covered many areas of antibiotic resistance, from both a scientific and philosophical perspective and addressed some of the problems encountered with new drug discovery and regulatory issues.

Highlights of the Presentation

The presentation began with a philosophical quote from Charles Darwin, which is as true today as it was when it was made in 1882, "It is not the strongest of species that survive, nor the most intelligent, but the ones most responsive to change". In the natural evolutionary competition for survival there is nothing that guarantees that the human species will be the survivor in our ongoing war against pathogenic bacteria. There is still much that we don't know about the natural world of microbes and the biologically active small molecules that they produce, a small percentage of which have antibiotic properties. The average streptomycete, for example, has the genetic capacity to produce about 30 complex small molecules, and there are more than 500 species of streptomyces alone. After a flurry of discovery in the 1940's, 50's and early 60's antibiotic discovery tailed off rapidly. There are a number of reasons why large pharmaceutical companies have essentially stopped research and development on new antibiotics including:



- Few new antibiotics have been found by traditional approaches
- Genomic approaches, such as high throughput screening, have not lived up to scientific or financial expectations
- Combichem libraries are limited sources of chemical diversity
- Companies are not convinced that new antibiotics are necessary when many of the existing ones still work very well

- It is very costly and time-consuming to develop new antibiotics and the financial return is not adequate when compared to the return on investment for drugs designed to treat chronic health conditions such as high cholesterol, heart disease and mental illness or 'quality of life' drugs such as Viagra
- Novel antibiotics are 'protected' to preserve their usefulness and are only used as a 'last resort', severely minimizing financial return
- FDA approval is arduous and risky, patents are short and often resistance to a new drug appears before the drug is even brought to market
- The high cost of drug production prohibits academic drug development through small biotech companies

Antibiotic resistance has always been present and the biochemical mechanisms involved are well understood. These mechanisms include target modification, by-pass, repair and amplification, decreased influx and increased efflux, enzymatic inactivation, sequestration, intracellular localization, and biofilm formation. Despite this knowledge however, resistance continues to be an increasing problem that has been exacerbated by the widespread use of antibiotics in agriculture. Recently, there has been a dramatic increase in research in this field, as measured by publications over the last two years, signaling an acknowledgment by the scientific research community that antibiotic resistance is becoming a serious health threat. Although Canada currently enjoys a lower rate of antibiotic resistance than the United States, this situation could soon change if we continue to ignore the warning signs and do not take better care of those effective antibiotics that we have. Possible solutions include:

- *Discovery of novel antimicrobials and their prudent use*
- *Alternative approaches (immunity, vaccines, phage, probiotics)*
- *Better understanding of pathogen, commensal and host biology, evolutionary development*
- *Increased surveillance and research on the epidemiology of resistance*
- *Improved public and healthcare specialist education*
- *Improved hygiene (back to Semmelweiss)*
- *Ban on non-therapeutic use of antimicrobials eg. in agriculture*
- *Reduce biocide (antimicrobial) use - reduce use of broad spectrum antibiotics which generate resistance faster*

There is no question that the discovery of antibiotics has had a major impact on public health and the control of infectious diseases caused by bacterial pathogens. Because antibiotics are easy to administer, act quickly and effectively, have limited side effects, are relatively inexpensive and can be assayed for activity, physicians have come to rely heavily upon them. It is incumbent on us to take the issue of antibiotic resistance seriously, act to mitigate its effects and provide clinicians with alternative approaches in the treatment of bacterial infections.

The Novel Alternatives to Antibiotics workshop was held at the Michael Smith Laboratories in Vancouver, British Columbia.

Break-out Sessions

Participants were divided into four groups, each facilitated by a member of the steering committee. Groups were provided with the following questions to guide their discussions:

- *What are the possible alternatives to antibiotics? Please list as many as you can.*
- *What are the Canadian research strengths and weaknesses for each alternative?*
- *What are the pros and cons of each topic as a feasible alternative to antibiotics?*
  i) in the short term - 0-5 years;
  ii) in the long term - over 5 years
- *What, in your opinion, are the three most important alternatives?*

Following the break-out sessions, the whole group re-convened and each working group presented an overview of their alternative approaches followed by a more detailed account of their discussions for each topic. As each topic was presented, the entire group was invited to contribute information and suggestions. By the end of the session we had a summary of all the possible alternatives proposed by the participants. Working group presentations were summarized on flip charts in point form:

Immune Systems:

Immune modulation, Vaccines - therapeutic and preventive;
Enhancement of innate immune response;
Anti-microbial peptides e.g. defensins;
Antibody therapy

- Enormous strength in immunology, untapped expertise, potential for new discoveries
- Need to link immunologists with microbiologists to combine strengths and expertise
- Therapeutic and preventive vaccines - vaccines to antibiotic resistance
- Immunotherapy - eg. monoclonal antibodies. Proven track record
- Suppression of inflammatory response - promotion of adaptive immunity
- Harness/boost innate immunity in both acute and chronic infections
- Study genetic factors, which are strong determinants of infectious disease
- Role of tumour necrosis factor (TNF)
- Variability in host colonization, host resistance, hidden streptomyces
- Need to develop mechanisms for rapid diagnosis - lab on a chip
- Use of other organisms to modify immune response
- Identification of new targets

Microbial Ecology:

Prebiotics - food , eg. non-digestible carbohydrate ingested by organism, not host
Probiotics - live microorganisms, health benefit, bacterial interference, competitive agents;
Alteration of bacterial flora, changes during disease

- Competitive agents, bacterial interference
- Strong base of expertise in microbial ecology, but not necessarily in health research sector
- Strong expertise in virulence mechanisms - could be combined with probiotics expertise
- Recombinant organisms to deliver things e.g. cytokines
- Probiotics not standardized, mechanisms poorly understood - more research in agriculture sector than health sector
- What can we deliver with probiotics eg. phages, cytokines
- Appropriate for many different infections
- Already using probiotics to treat C. difficile infections - need platform technologies
- Probiotics can be used in gut, vagina and topically

Bio-Prospecting:

- Many unidentified antibiotics already in libraries
- Create large libraries of small molecules, natural molecules with biological function and make publicly available - good area for discovery research
- Create libraries of microorganisms
- Tap into failed leads generated by pharmaceutical companies
- Proteomics - key enzymes, drugs
- Phage - mechanism of action for target identification
- Novel use of existing drugs eg. anti-depressants, anti-psychotics
- Lack of funds for screening, very expensive
- Need to engage chemists in translational research, chemical biology
- Drugs for targeting resistance - acquired and intrinsic

Phage Therapy:

- Specific therapy, not broad spectrum
- Long history, expertise in other countries eg. Russia
- Weak knowledge base in Canada - most expertise in agriculture and biotechnology
- Non-toxic, safe
- Could yield short term results
- Regulatory problems especially with phage cocktails
- Phage products eg. lysins are easier to work with than whole phages
- Need rapid diagnostics
- Strong potential for genetic engineering
- No effect on antibiotic resistance
- Already used successfully in some countries as a last resort
- Canada already using viral vectors in cancer therapy
- Need proof of concept studies eg. clinical trials

Novel Targets:

- Virulence resistance - eg. biofilm, modulators of immune response
- Novel targets lead to novel alternatives
- New targets necessary, eg. small molecules aimed at virulence mechanisms, rather than survival mechanisms
- Inhibit biofilm formation
- Inhibit virulence factors
- Strong expertise in bacterial pathogenesis, eg. CBDN
- Difficult to find funds for the translation piece - eg. screening of new leads

Physical Sciences:

Hyperbaric; Laser; Heat; UV;

Bio-Materials:

Prevent infection; Positive impact; Positive capacity; Positive mechanistic

- Research could yield short term results

Rapid Diagnostics:

- Need rapid diagnostics - tool development
- Point of care diagnostics - lab on a chip
- Rapid diagnosis would reduce inappropriate use of antibiotics and would permit use of narrow spectrum agents
- Not being done by private sector

Day 2 - March 11th, 2005

Following a brief summary of the points raised during the break-out sessions on Day 1, an open discussion was held with the whole group to further develop the ideas presented. The group referred to the following questions as a guide to discussion:

1. *Do we already have enough information to further develop the topic to create a research initiative? If not, what else do we need eg. an additional workshop with experts in the field? If so where will we find the expertise? - internationally? in Canadian research labs? Biotech companies? etc.?*
2. *Do we need to build research capacity? If so, what would be the best way to do this?*
3. *What kind of funding tools would be the most appropriate - consult CIHR funding sheet for guidance - eg. short term vs. long term programs, pilot projects, team grants, operating grants, training grants, RCTs, proof of principle etc?*
4. *What should the next steps be?*

It was decided that although bacterial diseases such as tuberculosis have a huge global impact they are currently not a big problem in Canada. Given the limited availability of funds, participants were advised to focus on antibacterial resistance from the Canadian perspective initially with a view to partnership in the international arena at a later stage. It was agreed that, in Canada, we are often out of synchronization with the research we fund relative to the actual disease burden and that we need better methods to track disease and define disease burden. This kind of information would be important to engage the interest of the Public Health Agency of Canada and Industry Canada but falls outside the mandate of this workshop. It was also decided that rapid diagnostics, although an important area of research and one that underpins the success of many alternative therapies, was not the focus of this workshop. There are already several existing funding avenues for this kind of research eg. CIHR operating grants.

Immune systems / Enhancing Innate Immunity

As one function of the immune system is to protect the host from infection, there was general agreement that modulation and enhancement of the host immune response would be a viable alternative to antibiotics either as an adjunct to controlled antibiotic use or in place of standard therapies. Participants were reminded that bacterial infections are not usually an acute life threatening event as in sepsis. More often, infections are chronic as in the case of wound infections, otitis and diarrhea and the window of opportunity for treatment can be several days or weeks, rather than hours. For example immunosuppressed cancer patients may respond over several days to growth factors given to stimulate neutrophil production and boost the immune response. To prevent post-surgical infections it might be possible to boost the immune response prior to surgery.

It was generally agreed that Canada has great strength in both immunology and microbiology but that the challenge is to get the two disciplines together. There were not many immunologists at the workshop although many were invited. The feeling was that they did not see the topic of the workshop as relevant to their area of research, but saw antibiotic resistance as being solely in the domain of the microbiologists. There is no shortage of potential interest and projects if the immunologists and microbiologists would work together.

Recommendations:

- Fund proof of principle research into mechanisms to modulate the innate immune response to better resist bacterial infection.
- Create research teams that combine the expertise of immunologists and microbiologists.
- As innate immunity falls off with aging, this might be a selling point to potential research funders, given the current demographics.

Therapeutic Vaccines

Proof of principle already exists in the vaccine area and there is already experience in therapeutic vaccines for cancer and more recently in dialysis and burn patients. There is even some evidence in early French literature for vaccines against S. aureus. More recently there has been research on an anti-toxin vaccine against C. difficile. There is also some evidence in mouse models for the efficacy of therapeutic vaccines and the discovery of new adjuvants may improve the effectiveness of experimental vaccines. However, there have been few studies relating specifically to vaccines against the handful of antibiotic resistant organisms.

Recommendations:

- The group recommended proof of concept studies on therapeutic vaccines both in animal and human models.
- It was noted that there is potential for partnership with biotech and vaccine research organizations such as CANVAC.

Microbial Ecology

Although Canada has significant research strength in microbial ecology, including expertise in biofilms and microbial genetics, there is little collaboration between researchers working with pathogens and those working with non-pathogens. Also little is known about the composition of natural flora occurring in the gut or vagina. It is therefore difficult to asses the effects of probiotics on natural flora. To fully explore these interactions, high throughput methods will be required to investigate the entire response. Therefore a team approach involving microbial ecologists, immunologists, microbiologists and probiotics experts will be required. Currently most of the Canadian expertise in probiotics resides in the agriculture sector, although probiotics have been used recently in the treatment of C.difficile infections in humans. One problem is the lack of standardization of probiotic products and regulatory constraints in administering probiotics to humans. One area of current research, pioneered at the University of Texas, involves the study of eukaryotic cells capable of producing of antibiotics that modulate the normal flora. Although traditionally associated with modulation of gut flora, probiotics may also have a role in the modulation of immune responses in the vagina and topically in superficial wound sites.

Recommendation:

- Participants recommended holding a focused workshop to bring people together in the area of probiotics research. This could be a joint venture by CIHR and NSERC. The focus of the meeting would be to combine clinical expertise with that existing in the agriculture and food sectors. It was suggested that the format of the meeting could be along the lines of the Application Development Workshop that III organized to prepare for the launch of the Safe Food and Water Initiative.

Bio-Prospecting

Antibiotics have been the biggest therapeutic success in history and continue to save millions of lives, but resistance has and always will be a problem with any new antibiotic. Discussion arose around the role of CIHR and other research funding agencies in the discovery and development of new small molecules with antibiotic activity. There are many failed leads in the archives of large pharmaceutical companies and the issue was raised as to whether it was a feasible role for academia to asses some of these undeveloped molecules. It was noted that the advice of the chemistry community would be needed to determine the value in pursuing this avenue of thought. It was suggested that a partnership between CIHR, NRC, NSERC and private industry would be most advantageous in exploring the diversity and efficacy of new small molecules from both existing libraries and new molecules discovered in the natural environment, eg. soil and oceans. It was noted that the NIH has made a large financial investment in the creation of chemical libraries.

Recommendations:

- It was agreed that the creation of chemical libraries (natural and man-made) and the screening and development of new drugs is a critical area that falls beyond the financial capability of any single organization. Although CIHR is beginning the process with the creation of the chemical biology network, there are currently insufficient funds to realize the full potential of such an endeavour.
- It was recommended that CIHR, NSERC and the NRC combine forces and approach private industry on this important topic with a view to forming a partnership for the joint screening and development of new small molecules with antibiotic activity.
- It was noted that, as with the development of any potential antibiotic therapy, it will be important to monitor the generation of resistance and devise methods to mitigate this effect.

Phage Therapy

It was acknowledged that there is little academic research in Canada on phage therapy although there are at least three Canadian biotechnology companies working in his area. Phage therapy was largely abandoned as a treatment for bacterial infection following the discovery of modern day antibiotics except in certain strongholds in Russia and Poland where phage therapy is reported to still be an accepted form of treatment for many infections. Recently, interest has been renewed in this largely abandoned area of research and with the increasing rise in antibiotic resistance, phage therapy may present a real alternative. Participants agreed that the scientific base in Canada is extremely weak and that the first task would be to build capacity and form collaborations with scientists from other countries such as Russia, Poland and to a lesser extent, the US. It was also acknowledged that given the increasing interest in phages as potential alternatives to antibiotics and the lack of current research capacity in Canada, this could represent an area where the fastest gains might occur, particularly in proof of concept studies eg. clinical trials. Development of this research area could be helped by collaboration with the agriculture sector which already has several successful models of using phage to treat infection in animals.

It was noted that one reason why phage therapy has not been adopted by private industry is the lack of potential for IP development. Discussion arose around the regulatory problems when using phage for human therapy especially if cocktails of many different phage are required. The point was made that viruses have already been approved for cancer treatment in certain circumstances so the regulatory hurdles could probably be overcome if the science was sound.

Recommmendations:

- It was recommended that collaborations be built with Health Canada, the agriculture community, biotech companies and phage researchers in Russia and Poland to further develop this topic.
- Also advice should be sought from Health Canada regulatory bodies regarding potential regulatory problems in the future.
- Proof of concept studies such as clinical trials were highly recommended.

Novel Targets

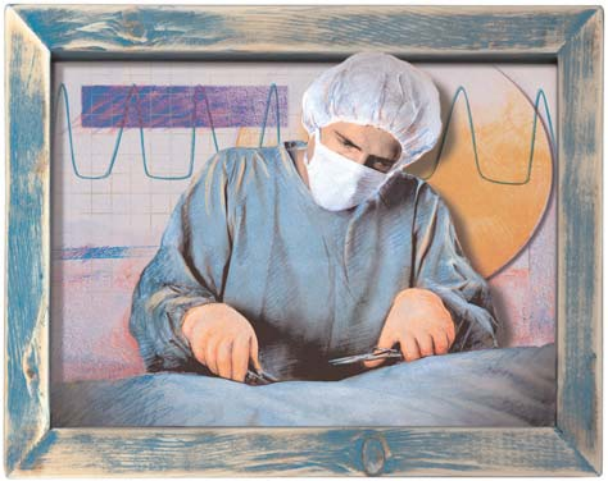
Participants felt that Canada already has strong expertise in the identification of new targets and that programs already exist for the adequate funding of research in this area, eg. through the CIHR operating grants competition and Proof of Principle program. What is really needed is a process to screen and develop potential new compounds with activity against specific novel targets, once identified. It is the translational piece that is missing.

Recommendation:

- Participants felt that this topic could be split between immune regulation and bio-prospecting, provided that emphasis was given to under-investigated targets such as virulence factors.

Physical Systems

Physical science refers to changes and modifications in the physical environment that may act to reduce the risk of bacterial infection or directly inhibit the growth of bacterial pathogens. This area includes advances in biomaterials research that may further reduce the risk of infection and need for pre- and post-operative antibiotics. Much of the activity in this area resides in small biotechnology companies as a relatively untapped resource. Examples range from raising patient (or environmental) temperature during surgery to reduce the risk of infection (syphilis was first cured by giving the patient malaria which raised their body temperature sufficiently to kill the syphilis bacterium!), to using UV light for water or surface sterilization. There are many promising technologies that are currently making few inroads into Canada.



Biomaterials

The development of biomaterials with built-in antibacterial activity is a huge and growing area that involves a host of different materials for different functions such as antiseptics, heavy metals, surfactants, anti-infective cement for implants, and ultra smooth materials for stitches and catheters that resist biofilm formation and eventually dissolve. There is already some limited expertise in Canada, but this area of research represents a field that is ripe for development and offers enormous potential for rapid commercialization of successful products. The area would be highly suitable for a partnership between CIHR, the NRC and NSERC.

Recommendation:

- This area looks at novel delivery systems rather that true alternatives to antibiotics, but any intervention that reduces the risk for infection also reduces the risk of resistance. This is an area that requires a novel, multidisciplinary research initiative focused on building capacity in the physical sciences and creating partnerships to study microbial events and develop new biomaterials that will reduce the need for antibiotics.

Next Steps

It was decided that as there are funds available immediately to support new research in this area (approximately $1 million per year for 5 years from III, plus contributions from partners), it would be possible to launch a request for applications (RFA) in the next six months to a year. There was support for a general approach that would not eliminate good ideas. The three main areas of research that emerged from the discussions as being of high priority and ready to be further developed were:

- modulation of the immune response,
- phage therapy
- physical science/biomaterials

It was felt that other areas such as probiotics and bio-prospecting would benefit from further discussion with experts and researchers from other disciplines. However, the group did not want to eliminate these areas from an RFA. It was suggested that the wording of the RFA should read, "areas of research including but not limited to immune modulation, phage therapy and physical sciences/biomaterials research". The RFA should list all the areas discussed during the workshop and should be linked to this workshop report.

It was agreed that the RFA should offer a variety of research funding tools, eg, short term programs such as Pilot Projects and Proof of Principle grants and longer term programs such as Team Grants and Randomized Control Trials (RCTs). The suggestion was also made that III could post a priority announcement in this area that applied to several of CIHR's open competitions eg. Operating Grants and RCTs.

There was strong support for a Letter of Intent (LOI) process on all grant applications, to ensure an acceptable success rate at the full application stage. It was recommended that in order to attract innovative and imaginative applications, applicants should be encouraged to state clearly in the LOI, how their research is novel and what the expected milestones are in both the short and long term. Applicants should also address the issue of knowledge translation and clearly state the expected outcomes of their research and how these outcomes will be moved into practice. Partnership will be strongly encouraged both between researchers with complementary expertise and between researchers and the private sector.

Participants were asked to complete a two-page workshop evaluation form before leaving the meeting. The results are given in Appendix 4.

The meeting was adjourned at noon and was followed by a two-hour meeting of the partner organizations to discuss opportunities for collaboration in the development of a Canadian research agenda on novel alternatives to antibiotics.

Appendices

Appendix 1 - Workshop Participants

NOVEL ALTERNATIVES TO ANTIBIOTICS WORKSHOP
MARCH 10-11, 2005

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Appendix 2 - Workshop Agenda

Novel Alternatives to Antibiotics Workshop

Thursday, March 10th, 2005
Michael Smith Laboratories
University of British Columbia
#301 - 2185 East Mall
Vancouver, V6T 1Z4

Day 1 – Thursday March 10th

Time	Item	Location
7h45	Bus departs from hotel	Westin Bayshore front lobby
8h30	**Registration/ Breakfast**	Michael Smith Laboratories Room 101
9h00	Welcoming remarks on behalf of CIHR-III ***B. Singh***	Michael Smith Laboratories Lecture Theatre (MSL 102)
9h10	***"Partnerships"*** ***J. Bray***	
9h25	***"Why are we all here?"*** ***B. Finlay***	Lecture Theatre (MSL 102)
9h45	***"Where are All The Antibiotics When You Really Need Them?"*** ***J. Davies***	Lecture Theatre (MSL 102)
10h30	**Health Break**	MSL 101
10h45	***"Changing The Rules – Eccentric Approaches to the Problem of Antimicrobial Resistance"*** Cancelled ***J. Hutchinson***	Lecture Theatre (MSL 102)
11h45	An Overview of Possibilities/ Logistics and Expectations of breakout sessions ***B. Finlay/ J. Bray***	Lecture Theatre (MSL 102)
Noon	**Lunch**	MSL 101
13h00	Breakout session: ➢ Identification of potential alternatives ➢ Discussion of relative strengths and weaknesses ➢ Prioritization for research development	Group A – MSL 201 Group B – MSL 203 Group C – MSL 237 Group D – MSL 303
14h30	**Health Break**	MSL 101
15h00	Group re-convenes Group presentations (15 min each) Discussion	MSL 102
16h30	Bus departs for hotel	Lobby
18h30	**Dinner**	**Shabusen Yakiniku House** 755 Burrard St 604-669-3883

Appendix 2 continued

Novel Alternatives to Antibiotics Workshop

Friday, March 11th, 2005
The Westin Bayshore Resort and Marina
1601 Bayshore Drive
Vancouver, V6G 2V4

Day 2 – Friday March 11th

Time	Item	Location
8h00	**Breakfast**	Oak Room
8h30	Summary of Day 1 ***J.Bray/ B.Finlay***	Oak Room
8h45	Open discussion (whole group): ➢ What do we still need to know? ➢ What is the research capacity and where is it located? ➢ What is the role of biotech? ➢ Do we need additional partners? ➢ What kind of funding programs will be required? ➢ What should the next steps be?	Oak Room
10h00	**Health Break**	Oak Room
10h30	Discussion (continued) Next Steps Summary ***B. Finlay/J. Bray***	Oak Room
noon	Meeting ends – hotel check-out	-
12h30 to 14h00	Partners' meeting "How can we best work together to implement the workshop recommendations?"	Fir Room

Appendix 3 - Biography

Appendix 3 - Biography

NOVEL ALTERNATIVES TO ANTIBIOTICS WORKSHOP
MARCH 10-11, 2005

Biography of Presenters

Dr. Julian Davies

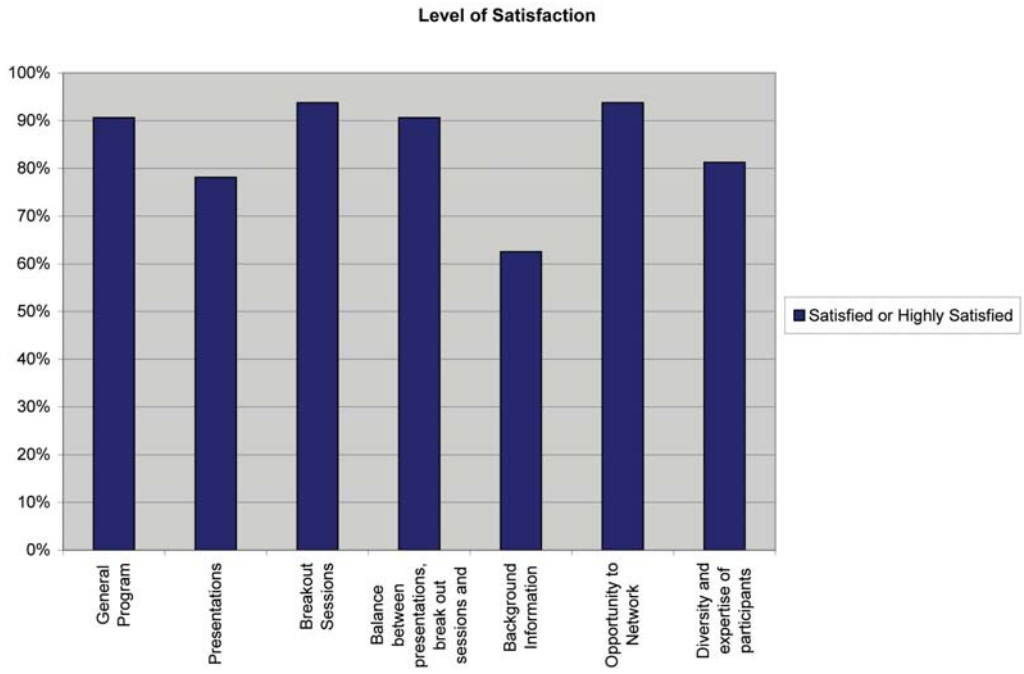
Department of Microbiology & Immunology
University of British Columbia

Dr. Julian Davies is Emeritus Professor of Microbiology and Immunology and Executive Vice President, Technology Development of Cubist Pharmaceuticals, Inc. Trained as an organic chemist, he switched to molecular microbiology in 1962 when he joined Harvard Medical School. Subsequently, he held academic positions at the University of Wisconsin, University of Geneva, and Institut Pasteur before joining the University of British Columbia as Head of Microbiology and Immunology in 1992. Davies was Research Director and President of of Biogen (Geneva) from 1980-1985 and founded TerraGen Discovery Inc (Vancouver) in 1996. He is a Fellow of the Royal Society (London) and the Royal Society of Canada. He is past President of the American Society for Microbiology. Dr. Davies' interests concern various aspects of microbial ecology. In particular, he has studied the origins and mechanisms of antibiotic resistance in bacteria, with special reference to gene capture and horizontal gene transfer. He is also studying the degradation pathways of xenobiotics and lignin-derived products by streptomycetes. The focus of work at Cubist Pharmaceuticals, Inc. (formerly TerraGen Discovery Inc.) is the study of microbes in the environment with special reference to the predominant non-cultivable species. Molecular techniques are being used to isolate genes for antibiotic biosynthetic pathways to study their expression in surrogate hosts with the goal of isolating novel secondary metabolites for pharmaceutical application.

Appendix 4 - Workshop Evaluation

Prior to leaving on Day 2, participants were asked to fill in a two-page workshop evaluation form. More than 90% of Day 2 participants returned their forms for a total of 32 completed evaluations.

Fig. 1 Results of Workshop Evaluation: Program



Overall, participants were satisfied or highly satisfied with all aspects of the workshop (see Fig. 1):

- 91% of respondents were satisfied or highly satisfied with the General Program.
- 78% of respondents were satisfied or highly satisfied with the Presentations.
- 94% of respondents were satisfied or highly satisfied with the Breakout Sessions.
- 91% of respondents were satisfied or highly satisfied with the Balance between presentations, break out sessions and open discussions.
- 63% of respondents were satisfied or highly satisfied with the Background Information.
- 94% of respondents were satisfied or highly satisfied with the Opportunity to Network.
- 81% or respondents were satisfied or highly satisfied with the Diversity and expertise of participants.

One identified area of weakness was the background information provided to participants prior to the workshop, as many felt that it would have been helpful to have received information on some of the potential alternatives to antibiotics such as probiotics and bacteriophages. However, the steering committee made a conscious decision not to provide this information to avoid influencing the direction of the discussions by pre-identifying specific alternatives. It was anticipated that workshop participants holding expertise in a specific area would share this expertise during group discussions, which did in fact seem to be the case in most instances.