NRC·CNRC
Biotechnology
Research Institute

Biotechnology Research Institute

A Global Player

2004/2005 Annual Report

National Research Council
Canada

Canada

A Word from the Director General

Although the life sciences sector in Canada posted a slight increase of 5% in venture capital investment in 2004, the money was invested in fewer companies, creating a very tight financing situation for small biotechnology players. Despite these unfavourable conditions, NRC's Biotechnology Research Institute was able to maintain a high level of academic and industrial R&D activities, allowing it to attain record revenues of $7.3 million in 2004-2005. This outstanding performance is attributable to the increase in contract-based collaborative activities with the industry and with other government departments.

The Institute also produced a larger number of scientific publications this year, totalling 138, and we granted seven patent licences to major players in the biotechnology and pharmaceutical sectors.

In partnership with our colleagues at McGill University (McDonald Campus) and John Abbott College, as well as at DSM Biologics and Laborium Biopharma™, we have developed a strategy to establish an integrated biomanufacturing complex. We have also renewed our agreement with Biophage Pharma Inc. to continue our research aimed at developing biosensors with biodiagnostics applications for the health, environment and industrial biotechnology fields. Another milestone in 2004: two years of work spearheaded by our scientists culminated in the complete annotation of the *Candida albicans* genome.

Once again this year, NRC-BRI hosted a large number of international and national events, including the annual meeting of the NRC's genomics program, with 215 attendees; the 4th annual Microarray Symposium, which brought together 375 participants, and the 10th annual *Crossroad of Biotechnology* conference, which was dedicated to biomanufacturing this year and drew more than 400 participants, including about a hundred from private sector companies. NRC-BRI also helped to organize the 10th World Congress on Anaerobic Digestion, which was held in Canada for the first time.

Finally, throughout the year, a number of NRC-BRI employees were actively involved in the NRC's strategic planning exercise, which should reach the implementation stage in 2006.

In light of the Institute's outstanding performance, we can look to the future with confidence!

Michel J. Desrochers
Director General

As a leading biotechnology research facility, NRC-BRI has earned an excellent reputation both nationally and internationally for the quality of its research and its support for the biotech industry.

The NRC's Biotechnology Research Institute: A Global Player

Over the past few decades, the field of biotechnology has experienced tremendous growth. Every year brings new biotechnology advances that enable us to answer questions, solve problems and rise to the challenges that society faces in the areas of health, agriculture and the environment.

The Biotechnology Research Institute of the National Research Council Canada is the largest biotechnology research centre in Canada. Located in Montreal—a major hub of the North American biotech and biopharmaceutical industry—the Institute carries out innovative research programs and contributes to the productive use of new knowledge in the health, bioprocessing and environmental protection fields. As a leading biotechnology research facility, NRC-BRI has earned an excellent reputation both nationally and internationally for the quality of its research and its support for the biotech industry.

Canada, which is currently home to 470 companies specializing in biotech fields, has the second highest number of biotechnology companies in the world, after the United States. Although almost 60% of Canada's biotechnology activities centre on health care, environmental biotechnology is expected to undergo considerable expansion given the challenges of meeting our sustainable development and climate change objectives, which will entail the development of new pollution prevention and mitigation technologies and the implementation of effective environmentally responsible industrial production practices.

Through its innovative biotech solutions, its technology transfer activities and its close involvement with industry in many collaborative research projects, NRC-BRI contributes to the development and commercialization of new technologies whose positive effects on health, the environment and the economy benefit Canadians and the international community.

2004-2005 Highlights

Financial Highlight

Outstanding Revenue Generation in 2004-2005
Despite the unfavourable climate that has persisted in the biotechnology field, NRC-BRI succeeded in generating more than $7.3M in revenues in 2004-2005, up $500K from 2003-2004 and $1.6M from 2002-2003.

Scientific Highlights

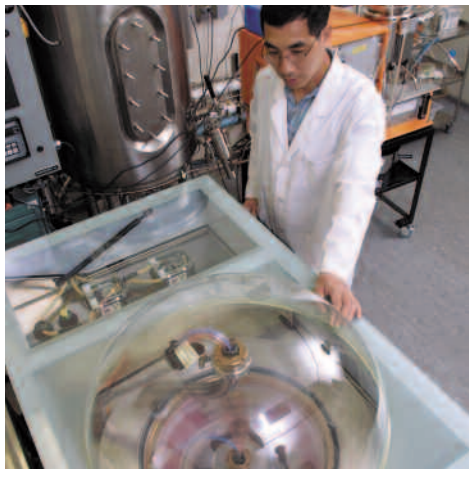
An Avenue for MTBE Degradation
The genes controlling an MTBE degradation pathway have been isolated from a strain of *Mycobacterium austroafricanum,* a bacterium that possesses the rare ability to use MTBE as a sole carbon and energy source. The genes have been sequenced and expressed in a heterologous micro-organism in order to confirm their role. A biological barrier using this micro-organism has also been developed for the bioremediation of MTBE-contaminated water sources.

Fluorescence for Bioprocess Monitoring
A multiwavelength fluorometric system has been developed for real-time bioprocess monitoring. This innovative system, combining *in situ* fluorescence measurements and sophisticated statistical analyses, provides a reliable method for online analysis and evaluation of the concentration of components in liquids resulting from production processes or wastewater treatment in a bioreactor.

A Microarray for Pathogen Detection
A microarray designed to detect and identify virulence factors and resistance genes associated with potentially pathogenic strains of *Escherichia coli* has been used to analyse water quality in a Canadian harbour. Surprisingly, more than 30% of the strains inventoried were found to contain pathogenicity markers.

Production of Third-Generation Viral Vectors
A new strategy for producing third-generation adenoviral vectors that are compatible with gene therapy applications has been validated. The production steps have been optimized to reduce the risk of undesirable recombination events, to minimize helper-virus contamination and to increase yield.

First Step Toward the Development of Personalized Medicine
Antibodies directed against clusterin, an effector that acts downstream of the TGF-ß pathway, have been produced. These antibodies, which can be used to specifically recognize this tumour marker, neutralize the promoting activity of TGF-ß in a number of cancer cell lines. This technology represents a first step toward the development of personalized medicine combining molecular diagnostics and therapy.



The Health Sector has eight research groups whose work centres on two of the leading causes of death and disease worldwide: cancer and infectious diseases.

Health Sector

The Health Sector, a key research component at the Biotechnology Research Institute, has eight research groups whose work centres on two of the leading causes of death and disease worldwide: cancer and infectious diseases. The Health Sector's researchers use their knowledge and resources to identify and characterize molecular targets in cancer cells, to gain a better understanding of the causal agents of infectious diseases and to support drug discovery, development and validation. The Sector's research groups apply a number of experimental approaches, such as genomics, proteomics, combinatorial chemistry, structural biology, polypeptide engineering and bioinformatics, to attain their objectives.

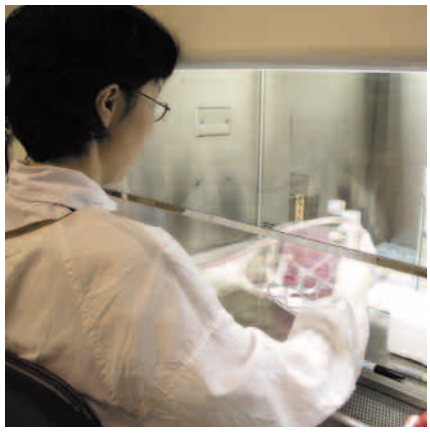
Research Programs

Cancer

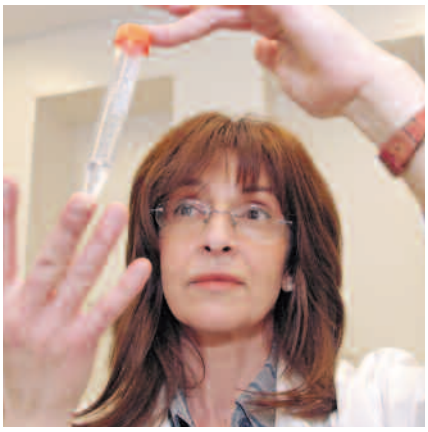
Cancer occurs when normal cellular processes that control cell's growth, division and death, go awry. Although genes within the cell normally regulate these processes, mutations or errors in the cell's genetic code can lead to rapid and uncontrolled cell division, resulting in cancer. Factors such as heredity, age and the environment contribute to these changes in the genetic code. Prostate cancer in men and breast cancer in women are among the most frequently diagnosed types of cancer. Lung cancer, although less common, is currently the leading cause of cancer deaths. The Health Sector's cancer research program focuses primarily on breast cancer, but also targets both prostate and lung cancer. The main objective of the program is to develop linkages between molecular diagnostics, imaging and therapy. Efforts are devoted to identifying tumour markers that can aid in early detection and monitoring of disease processes as well as response to treatment. Potential therapeutic targets that can serve simultaneously as markers are also sought. Among these targets and markers of interest, the Health Sector's research groups are currently evaluating the role of proteases (cathepsin B, L and X) in cancer and seeking to characterize the molecular mechanisms underlying growth factor (TGF-ß, EGF) induced tumourigenesis.

Infectious Diseases

The advent of vaccination programs and antibiotics had, by the mid-20th century, prompted the prediction that most infectious diseases would be brought



under control or even eradicated by now. The emergence of new diseases like SARS, avian influenza, AIDS and hepatitis C; the re-emergence of diseases such as tuberculosis and malaria; and the rapid development of antibiotic resistance in some micro-organisms have disproved this prediction. Consequently, infectious



diseases are still a major public health threat today. Every year, more than 15 million people die from infectious diseases while several million people will survive with lingering health problems. There is a pressing need to identify new targets and new molecules that can be used to combat pathogenic bacteria, fungi and viruses.

Under the Health Sector's infectious disease program, research focuses on two areas: revealing the molecular mechanisms involved in the pathogenesis of *Candida albicans,* a yeast-like fungus that can cause a lethal infection in immunocompromised individuals, and identifying potential virulence factors in pathogenic bacteria. By combining genomics and structural and cellular biology techniques, the research groups conduct studies to characterize this fungal pathogen from a molecular standpoint, elucidate its interaction with the host and identify new targets for therapeutic interventions.

An understanding of the virulence mechanisms associated with infectious agents is crucial for developing control strategies. The Sector's research groups therefore use state-of-the-art technologies such as NMR and crystallography to establish the three-dimensional structures of virulence factors from pathogenic strains of bacteria. The goal is to identify these proteins' substrate binding sites, characterize their mode of action and, ultimately, develop inhibitors.

Major Advances

Clusterin Antibodies: A Novel Tool for Diagnostics and Therapy

Transforming growth factor-beta (TGF-ß) is the member of a large family of signalling molecules. These multifunctional peptides play an important role in controlling cellular development processes, growth and homeostasis in most tissues. An inhibitor of epithelial cell proliferation, TGF-ß acts as a natural suppressor in the early stage of tumour formation. Nonetheless, there is increasingly strong evidence that TGF-ß can promote tumour progression and metastasis in the advanced stages of development of some cancer cells. This dual role (suppressor and promoter) is of primary importance for developing therapies targeting the signalling pathway of TGF-ß. In fact, inhibitors directed at this pathway might inhibit metastasis but accelerate the development of early lesions.

With the aim of discovering safer targets for designing therapeutics, the Receptors, Signaling and Proteomics group has been working to identify effector molecules that act downstream from the TGF-ß promoting pathway. The researchers have succeeded in identifying a new effector of this pathway: clusterin. This constitutive protein is suspected to be implicated in the process of apoptosis and in cellular protection mechanisms. Clusterin overexpression in cancer cells has been linked to both the body's natural anti-tumour defenses and chemotherapeutic agents. The ability to modulate clusterin activity or expression therefore represents an avenue for developing new therapeutic and diagnostic approaches. Accordingly, clusterin antibodies have been produced, making it possible to identify the epitope of clusterin which is responsible for its tumour-promoting activity. Our researchers have also shown that these antibodies neutralize the promoting activity of TGF-ß and clusterin in breast and prostate cancer cell lines of murine and human origin. Consequently, these antibodies could represent a novel therapeutic approach for controlling tumour progression and reducing the associated capacity to promote metastasis. Moreover, these same antibodies might be able to serve as diagnostic tools for detecting and monitoring tumours. This potential linkage between therapy and diagnostics might be a significant step towards personalized cancer treatment.

In 2002, the Genetics group of the Health Sector began co-ordinating an international effort to decode and fully annotate the genome of *Candida albicans*; the goal was reached in 2004.

Identifiying the Genes of a Pathogenic Yeast-Like Fongus

Candida albicans is a fungus that is part of the normal microflora of the human body. Under certain conditions, however, this micro-organism can become an infectious agent. In healthy individuals, the infections it causes are usually limited to the mucous membranes. Severe and potentially fatal systemic infections can, however, develop in people whose immune system is compromised. Since the number of people with depressed immune systems is on the rise because of the spread of HIV infection and the increased number of individuals undergoing cancer therapy, this micro-organism is now the main cause of fungal infections in humans. Despite the prevalence of this pathogen, there are few weapons for fighting it. Research into the genome of *Candida albicans* should aid in turning the situation around.

In 2002, the Genetics group of the Health Sector began co-ordinating an international effort to decode and fully annotate the genome of *Candida albicans*. The ultimate goal of this co-operative project was reached in 2004 with the unveiling of detailed data on the 6,354 genes in the genome of this micro-organism. Since the genome contains all

the instructions (genes) necessary for the development and functioning of *Candida albicans,* we now have the ability to identify the genes specific to this fungus. This will help us gain a better understanding of it and assist in developing safer and more effective drugs. Exhaustive comparative analysis have enabled the Genetics group to identify 228 genes of *C. albicans*— which are also present in the five other known fungal genomes—for which there is no homologue in the mouse or human genome. Each of these genes represents a potential target for the development of new antifungal treatments. The comparative studies of fungal genomes have also revealed that *C. albicans* has a capacity for adaptation which may increase its propensity to invade host tissues in order to meet its nutritional requirements. In fact, the group has identified a multitude of genes in this fungus that may be involved in the secretion of proteolytic and lipolytic enzymes or the expression of nutrient transporters and cell surface receptors. These are just two of the many avenues that may be explored as part of the effort to combat this serious human pathogen.

The SARS Coronavirus: Pathogenicity and Inhibition

In recent decades, more than 30 new infectious diseases have been identified. One of these—Severe Acute Respiratory Syndrome or SARS—has revealed the global health threat associated with infectious diseases that have the ability to emerge and spread rapidly. In just a few months, more than 8,000 people were infected with SARS and more than 80 deaths were reported in the thirty or so countries affected. SARS is a respiratory infection caused by a previously unrecognized virus from the coronavirus family. The genome of this RNA virus encodes two polyproteins. Proteolytic cleavage of these two precursor polyproteins into smaller individual protein units is required for viral replication and maturation. The viral proteases PLpro and 3CLpro perform this cleavage. Since these proteases constitute potential targets for antiviral drugs, learning more about them is an important step toward developing SARS treatment strategies.

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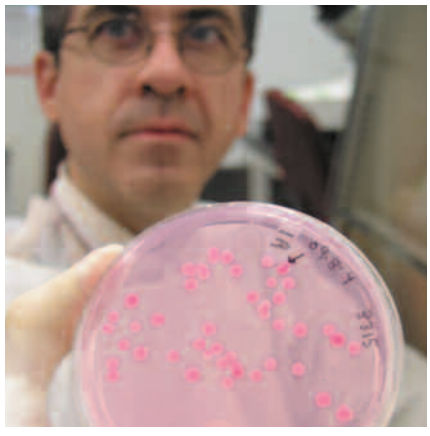

The Computational Chemistry and Biology group and the Enzymology group have carried out an in-depth characterization of the structures and functions of the SARS-coronavirus PLpro. This involved building a structural model of a coronavirus PLpro by using leading-edge bioinformatics techniques to derive important information about the molecular foundations of this enzyme's functions during the viral maturation process. This information will be used in drug development efforts. Even more importantly, the three-dimensional model made it possible to predict a previously unsuspected biological function of this protein, namely deubiquitination. This is only the second known example of this type of activity in a viral protein and it represents a first for the coronavirus. This prediction has given rise to interesting hypotheses about the pathogenicity of the SARS virus. In fact, this activity could be linked to a mechanism for evading the host immune response. The other protease of interest, 3CLpro, is also a key target for antiviral drug development. Following *in vitro* identification of some promising compounds, the Computational Chemistry and Biology group undertook to evaluate these substances and their analogues through cell-based assays. A number of these inhibitor compounds have been found to reduce viral replication substantially. The discovery of PLpro's deubiquitination activity and of the critical role that these proteases—3CLpro and PLpro—play in the life cycle of the human SARS coronavirus makes these enzymes highly strategic targets for fighting this emerging disease.

Ongoing Research

Over the past year, our cancer and infectious disease research programs have chalked up some major achievements. An efficient method for mass bacterial production of small interfering RNAs (siRNAs) and short hairpin RNAs (shRNAs) has been developed. This technology will help to expedite functional genomics studies and to develop RNAi-based novel drugs. In a drug-repositioning project, our researchers have shown that tetracyclines can be changed into specific inhibitors of calpain proteases. These enzymes are potential therapeutic targets for treating infections, strokes and cancers. The structural proteomics platform has made it possible to establish the three-dimensional structure of heparinase II in a complex with a disaccharide product. This achievement provides a basis for designing variants of this enzyme which is widely used for the chemical analysis of complex glycosaminoglycans.

The Bioprocess Sector uses a wide range of technologies including microbial fermentation, cell culture, biocatalysis and bioreactors to produce therapeutic bioproducts.

Bioprocess Sector

The Bioprocess Sector uses microbial, animal and human cells as well as enzymes and gene transfer vectors in developing innovative biotechnology products and processes. The Sector's multidisciplinary teams use their expertise and the Institute's leading-edge facilities to assist the biotechnology industry and the broader research community in developing, optimizing and scaling-up bioprocesses for production and purification. A wide range of technologies including microbial fermentation, cell culture, biocatalysis and bioreactors are used to produce therapeutic bioproducts such as vaccines, monoclonal antibodies, vitamins and hormones, as well as industrial bioproducts such as bioplastics and insecticides.

Research Program

Bioprocesses Development

Thanks to advances in molecular biology, live cells can be directed to perform certain useful functions. Researchers have adapted bacteria, yeasts, as well as insect, animal and human cells to turn them into living "factories" for the production of chemical compounds or recombinant proteins. In the field of chemistry as in the food and health sectors, there are many potential applications for this technology. The primary aim of the NRC-BRI's bioprocess research program is to optimize the use of a variety of host cells and their components in order to develop innovative products.
The Bioprocess Sector has achieved recognition for its expertise in designing unique expression vectors and developing, optimizing and scaling-up bioprocesses. Gene therapy is an area in which the Sector is especially active. This field is generating considerable interest on the international scene at present, with the many clinical trials that are under way, and there are promising opportunities for vector design and optimization as well as production.

Major Advances

Refinement of the Cumate Switch

Recombinant DNA technology allows the production of foreign proteins into micro-organisms or eukaryotic cells. Depending on the approach used, protein synthesis may be either constitutive or inducible. During constitutive synthesis, the foreign protein is produced continuously. In some circumstances, such as when the foreign protein is poorly tolerated by the host cell, it is helpful to be able to control the timing, duration or level of production of the protein. Inducible expression systems are designed to provide this kind of

control in response to the presence or absence of a specific regulator, called the inducer. Inducible systems are of limited use in mammalian cells because of the side effects associated with the inducers, the low level of expression achieved and their inability to tightly regulate the inducible expression.

The versatility of the cumate switch was demonstrated: it performs well in both mammalian cells and bacterial cells.

In recent years, the Genomics and Gene Therapy Vectors group has developed and optimized an inducible expression system—a cumate switch—whose genetic constituents are from the bacterium *Pseudomonas putida* F1. Various applications have recently pointed up the usefulness of this system for producing recombinant proteins in mammalian cells. A CHO cell line that stably expresses the cTA transactivator of cumate has been produced (CHO-cTA). With this cell line, researchers have been able to achieve the stable production of 500 mg per litre of recombinant antibodies using a batch culture in chemically defined serum-free medium. This new cell line (CHO-cTA) has also been modified to make it permissive to adenovirus infection. To enable this, the gene encoding the adenovirus primary receptor (CAR) was inserted into these cells to ensure stable CAR expression. The research team has shown that, following infection with an adenovirus vector, the CHO-cTA-CAR cells are able to attain high recombinant protein yields (100 mg per litre) in serum-free medium.

In addition, the Enzymatic and Microbial Technology group has demonstrated the versatility of the cumate switch through its pioneering efforts in developing the first practical gene switch capable of directing the inducible expression of recombinant proteins in the methylotrophic bacterium *Methylobacterium extorquens* (ATCC 55366). The group possesses a gene switch that performs well in both mammalian cells and bacterial cells. This team of scientists also developed a methodology for multicopy integration of heterologous genes and their stable expression in *M. extorquens*. This new technology does not require the use of antibiotic resistance genes and it allows modulation of the expression level. Interestingly, integration occurs at a unique and specific integration locus on the chromosome. The recent results obtained with *M. extorquens* will greatly facilitate future metabolic engineering activities using this bacterium.

Innovative System for Using Insects Cells in Recombinant Protein Production

Insect cells are frequently used in biotechnology to produce recombinant proteins. Insect baculoviruses are typically used to produce vectors for inserting genes of interest into insect cells and inducing their expression. These baculovirus expression systems are typically used as a laboratory tool, although they also hold promise for the production of vaccines and diagnostic reagents. Insect cells offer several clear-cut benefits: high production yields, rapid growth in suspension culture and ability to perform most translational modifications. A major drawback remains in relation to the use of a baculovirus to insert a desired gene: recombinant protein production takes place only for a limited time because replication of the baculovirus induces cell lysis.

The Animal Cell Technology group has developed insect cell lines that permit the stable expression of proteins of interest. These cell lines are obtained by transfecting *Spodoptera frugiperda* (Sf-9) cells or *Trichoplusia ni* (High-Five™) cells. This transfection, performed without the baculovirus system, is followed by stable integration of the gene of interest, coupled to a strong promoter, within the host cell's genome. These cell lines have been used to develop the first perfusion process for producing recombinant proteins using an insect cell expression system. The group has harnessed its expertise related to the critical operating parameters of the acoustic filter-based perfusion process in seeking to maximize the yield obtained from this process. This filter approach offers several advantages: reliable cell retention, reduced hydrodynamic stress exerted on cells and low risk of clogging. In addition, the group has used knowledge acquired from analysing the metabolism of the main carbon and energy sources in insect cells—glucose and glutamine—to rationally define the composition of the culture medium and the feeding strategy used during the perfusion process. These advances, coupled with the novel capacity offered by stable insect cell lines, have enabled the researchers to develop, optimize and apply an acoustic filter-based perfusion process to produce recombinant proteins. The long-term stability and robustness of this process have been demonstrated through the production of green fluorescence protein (GFP) and various therapeutic proteins at scales of up to 20 litres. These characteristics, combined with the high cellular density and high yield obtained, confirm the potential that this new technology offers for the production of recombinant proteins, virus-like particles and adeno-associated viruses.

Strategy for Producing Third Generation Adeno-Associated Viruses

Viruses have developed strategies for inserting their genetic material into host cells in order to replicate. Scientists are seeking to capitalize on this ability through gene therapy approaches. Gene therapy involves converting suitable viruses into vehicles, or vectors, that are capable of targeting and safely delivering a specific "repair" gene to a person's cells. The adenovirus is one of the viruses used widely for this purpose, and three generations of adenoviral vectors have been developed to date. The first and second generations elicit an immune response that reduces their effectiveness and hence their use. By contrast, the third generation, of so-called "gutted" vectors, has low immunogenicity and a greater

cloning ability than the early-generation vectors. However, the production of gutted vectors remains problematic.

The Animal Cell Technology group has developed a strategy for producing third-generation adenoviral vectors. After modifying a human cell line, the group carried out work to optimize the initial production stages. The production process typically begins with transfection of the genome of the gutted vector and the helper virus into the host cells, followed by successive cell passages. These repeated cell passages are necessary to obtain a sufficient quantity of gutted vectors to permit a high production scale. One of the key innovations of the present strategy is that it minimizes the number of cell passages required to obtain enough vectors to start up bioreactor production. Since each passage can be accompanied by harmful and cumulative recombination events, reducing the number of cell passages is crucial for developing an effective method for third-generation adenoviral vector production. As part of an effort to perfect the production process, the strategy developed also uses serum-free suspension cultures, selective encapsidation of the gutted vector against the helper virus and an optimized purification process. Validation of the production and purification processes at a three-litre scale has demonstrated the system's capacity to produce third-generation adenoviral vectors that are compatible for gene therapy use.

High-Throuphput Recombinant Protein Production

Natural proteins suitable for medical use, such as Factor VIII for haemophiliacs and insulin for diabetics, used to be extracted from biological fluids or organs. These extraction methods were very inconvenient, however, owing to limited availability and the risk of contamination from proteins obtained from subjects with undetected illnesses. Recombinant protein technology now permits the production of safe and effective therapeutic proteins in abundant

quantities. Insulin, interferon, erythropoietin and monoclonal antibodies are examples of the recombinant proteins that are now used in humans. Mammalian and human cells are ideal hosts for recombinant protein production because they allow complete maturation of desired proteins. Despite numerous advances, recombinant protein production processes using human cells still need to be perfected.

During the past year, the Animal Cell Technology group has continued work to enhance its recombinant protein production process using a proprietary human cell line (HEK293) in serum-free medium. These efforts have brought about an appreciable increase in cell density, production scale, recombinant protein yield and product quality. Improvements have been made in the expression vector, the cell line and the processes. Optimization of the transfection technique, rational design of the culture medium and the development and use of advanced methods and systems for online control and monitoring were critical success factors in this undertaking. With this robust large-scale transfection and production technology, recombinant protein yields as great as 150 mg per litre have been produced from complementary DNA, in less than three weeks. Over the past year, this technology has been routinely used to produce a wide range of secreted, intracellular and membrane-bound proteins, at scales of up to 40 litres. This optimized process may not only have numerous applications for producing complex proteins such as monoclonal antibodies, it may prove useful for generating viral vectors, such as adeno-associated viruses and lentiviruses, for gene therapy applications.

Ongoing Research

Over the past year, Bioprocess Sector groups have made some important scientific and technological advances, which include contributions to several external research projects. For instance, the protocol for the purification of lactoferrin has been greatly improved, thereby benefiting a small Canadian company. The new protocol yields lactoferrin that is essentially protease-free and about 99% pure. Lactoferrin is a protein that shows activity against viruses and various types of cells, including cancer cells.

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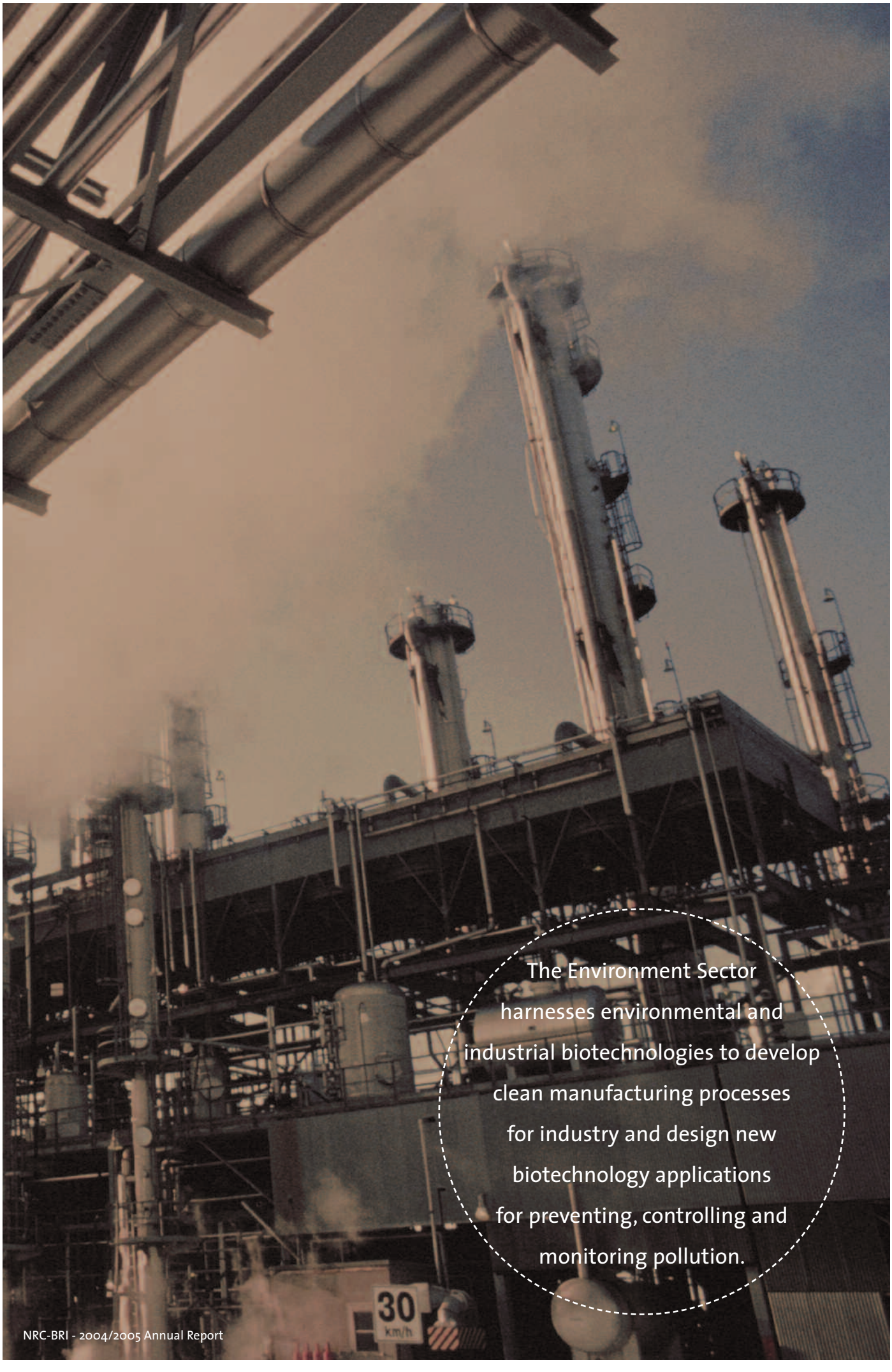
Efforts have also been devoted to producing and purifying a bacteriocin, pediocin PA-1, to support additional screening activities. Assays conducted with cancer cell lines have permitted the preliminary identification of promising antitumoural activity. The Sector's scientific expertise has also been harnessed in developing a new packaging cell line that permits efficient and large-scale production of regulated, conditional self-inactivating (SIN) lentiviral vectors in serum-free media.



The Environment Sector harnesses environmental and industrial biotechnologies to develop clean manufacturing processes for industry and design new biotechnology applications for preventing, controlling and monitoring pollution.

Environment Sector

Human activities have a range of negative impacts on the biosphere: global warming, water pollution, reduction in biodiversity, depletion of the ozone layer, acid precipitation, desertification and deforestation. Through its two research programs—environmental protection and eco-efficent industrial production —the Environment Sector harnesses environmental and industrial biotechnologies to develop clean manufacturing processes for industry and design new biotechnology applications for preventing, controlling and monitoring pollution. Supported by the expertise of its seven research groups, the Sector uses advanced biotechnology techniques and leading-edge infrastructures to develop solutions in order to reduce pressure on natural resources and achieve the protection, clean-up and monitoring of water, soil and air.

Research Programs

Environmental Protection

Maintaining the ecological balance and integrity of the planet's soil, water and air is of crucial importance for meeting present needs without compromising our ability to meet the needs of future generations. Over the past 40 years, resource development and consumption have reached an unprecedented scale, resulting in the depletion of natural resources, threats to fish stocks, growing volumes of waste, lowering of water tables, melting of the polar ice caps and an accelerated rate of deforestation. Some of the damage caused to the environment has direct implications for human health. For example, chemical and bacterial pollutants make their way into water reserves, the atmosphere and food sources, and this contamination kills several million people every year, especially in developing countries.

The environmental protection program, which supports the objectives of sustainable development, tackles these issues through the work done by the Environment Sector's researchers with expertise in the treatment and monitoring of contaminated soils, groundwater, sediments, air as well as industrial waste waters. The Sector's multidisciplinary team of scientists and engineers work closely with industry in research and development initiatives centring on innovative environmental technologies for remediating contaminated sites, studying microbial communities and their response to major environmental problems (climate change, toxic emissions) as well as detecting pathogens and environmental contaminants in food, water and soil resources.

Eco-Efficient Industrial Production

Although industrial development can raise the standard of living for some segments of the world's population, increases in production and consumption lead to a major deterioration of the environment and reduce the quality of life for many individuals. This is obvious when we consider nature's limited capacity for

renewal and ecosystems' limited ability to absorb polluting emissions like greenhouse gases. The implementation of the Kyoto Protocol and efforts to raise awareness among businesses and government of the importance of sustainable development constitute initial steps toward finding solutions.

Eco-efficiency—a concept that relates to natural resource use and the effect that industrial systems of production and consumption have on resources—is one of the avenues put forward for solving environmental issues. This approach calls for the adoption of cleaner technologies and changes in manufacturing processes to reduce releases of gases and toxic substances, optimize the use of natural resources (using renewable resources, energy efficiency, etc.) as well as increase the potential for recycling materials and extending the service life of products. The Environment Sector's clean manufacturing program harnesses the multidisciplinary expertise of its researchers in evaluating the eco-efficiency of new products and processes, devising ways to use biomass and developing rigorously controlled industrial processes that use fewer resources and produce less waste and pollution.

Major Advances

Monitoring Waterborne Pathogens

The presence of pathogens in water sources used to supply water for drinking, food preparation, bathing and recreational activities can have a serious impact on human health. A number of bacteria, viruses and protozoans in the water can cause infections; they typically enter water supplies through wastewater discharges, agricultural run-off or wildlife use of water bodies. It is therefore of paramount importance for public health agencies to have appropriate tests for detecting waterborne pathogens.

The Environmental Genetics group develops DNA microarrays for the rapid and precise detection and identification of pathogens in the environment. *Escherichia coli,* a common intestinal bacterium in humans and animals, is usually harmless; however, some pathogenic strains of this bacterium can kill people. Over the past few years, the group has developed a microarray specific to pathogenic strains of *E. coli*. Thanks to enhancements, this microarray now encompasses more than 30 antibiotic resistance genes, 130 virulence genes as well as their variants that are specific to certain hosts. Made in collaboration with Environment Canada, a study on water contamination in Hamilton harbour has yielded some surprising results. More than 30% of the *E. coli* strains identified were found to be potentially pathogenic. The researchers also noted a significant difference between the pathogens present in spring and summer. An impact assessment is currently being carried out on human and avian sources of contamination of the water at this harbour and at nearby beaches. The microarray's ability to identify the source of contamination is important, as it will aid in developing more effective prevention and clean-up measures.

Biodegradation of MTBE-Contaminated Groundwater

Methyl tertiary-butyl ether (MTBE) is a fuel additive that is used to reduce emissions of carbon and unburned hydrocarbons. Every year, 20 million tonnes of MTBE are used worldwide. Because this substance is highly water soluble and because gasoline spills frequently enter the soil, many aquifers are already contaminated with MTBE. MTBE's unpleasant taste, its persistence and the limited knowledge about the human health effects of ingesting low levels of this chemical point up the need to develop measures for removing it from groundwater supplies. Since physico-chemical degradation procedures are not very effective, microbial processes appear to be the most promising avenue in this regard.

New data show that efforts can now move forward to design and implement effective bioremediation strategies for removing MTBE from aquifers.

The NRC-BRI's Environmental Microbiology and Environmental Bioengineering groups, working with researchers from the *Institut Français du Pétrole (IFP),* have made some advances in the area of natural attenuation of MTBE. This progress can be attributed to the IFP researchers' success in isolating one of the first micro-organisms with the ability to use MTBE as a sole source of carbon and energy, namely *Mycobacterium austroafricanum*. This metabolic function gives the bacterium the ability to achieve complete mineralization of this organic pollutant, which means that it can transform the compound into water and carbon dioxide. The Environmental Microbiology group has studied the pathways of MTBE degradation in *M. austroafricanum* at the molecular level. As a result, a group of genes whose expression is induced when the micro-organism is grown on a medium having MTBE as the sole carbon source has been cloned, sequenced and expressed in *M. smegmatis*. These are the first genes linked to an MTBE degradation pathway that have been cloned and expressed in a heterologous bacterium in order to confirm their role. Characterization of the genes has provided an important tool for identifying other micro-organisms with the ability to mineralize MTBE and studying the distribution of such micro-organisms in the environment.

Meanwhile, the Environmental Bioengineering group has developed and established the main parameters required for the application of a process employing *M. austroafricanum* to bioremediate MTBE-contaminated water sources. This process, which operates as a biological barrier, has proven very effective in removing MTBE from water under laboratory conditions. The data obtained show that efforts can now move forward to design and implement

effective bioremediation strategies for removing this potentially carcinogenic contaminant from aquifers.

Understanding the Environmental Fate and Effects of a New Substance

Nitramines are the most recently introduced class of organic nitrate explosives, and CL-20 is one of the high-energy explosives that fall into this class. First synthesized in 1987, CL-20 is slated to come into use as a replacement for RDX and HMX (two other explosives in the class) because it is more stable and powerful. Since the introduction of compounds such as RDX and HMX led to contamination of soil and groundwater sources in the past, it is important to determine whether CL-20 and its degradation products have adverse effects on human health and the environment before it comes into wider use.

The Environmental Chemistry and Applied Ecotoxicology groups have conducted research into the migration and degradation of CL-20. The researchers have identified the mechanisms governing the migration of this compound in soil-water systems down to the water table and determined the chemical and microbial degradation pathways. Following the development of analytical tools for quantifying CL-20 and its degradation products in water and soils, the group adopted an approach combining microbiology and chemistry. More specifically, the techniques of analytical chemistry and microecosystem research were used together in identifying a number of CL-20 degradation pathways. Chemical (or abiotic) degradation pathways, as represented by photodegradation and degradation by zero-valence iron, have been characterized, as have the biotic, aerobic and anerobic degradation pathways associated with microbial communities and isolates. The group has also successfully converted CL-20 back into glyoxal, the starting compound. Knowledge acquired about the CL-20 degradation pathways will enable us to gain insight into the mechanisms underlying the transport and fate of this compound and to predict its toxic effects on human health and on aquatic and terrestrial ecosystems. Furthermore, this new knowledge provides the basis for designing, optimizing and monitoring future bioremediation strategies for CL-20-contaminated environments.

Improving Bioprocess Control Through Real-Time Measurement

Careful control of bioprocesses is essential in order to maximize their efficiency. Online process monitoring, control and fault detection all depend on reliable real-time measurements. Online monitoring is usually limited to measuring biogases, whereas offline methods need to be used to measure key parameters like product and substrate concentration. In addition to involving significant time lags between sampling and availability of results, offline methods do not permit rapid detection of imbalances and metabolic activity during the process. This ultimately leads to poorly timed diagnostic procedures and limited process control capacity. Instantaneous and accurate online measurements are therefore of the utmost importance for the bioprocess industry.

The Environmental Bioengineering group has developed an innovative real-time bioprocess monitoring system that uses multiwavelength spectrofluorometry, in combination with regression models, to study the *in situ* concentration of key constituents of the liquid phase such as the substrate, the degradation products or the final product during anaerobic digestion processes. A LED light source coupled to a CCD array spectrometer is used to measure and acquire fluorescence spectra; this architecture has the advantage of reducing response time and equipment costs. Since multivariate analysis is required to determine the linear relationship between the analytical measures and the multiwavelength spectra, various methods have been tested in order to develop the regression model. The partial least squares (PLS) multivariate statistical algorithm has proven to be the most reliable approach for predicting the composition of the waters tested. The multiwavelength fluorometric system has been used successfully for real-time monitoring of laboratory-scale anaerobic fermentation and digestion. More recently, the system has been used for the real-time measurement of chemical oxygen demand and volatile fatty acid concentration in a wastewater treatment plant, demonstrating its effectiveness in an industrial setting. It therefore represents an innovative and efficient solution for companies whose biotechnology production processes or wastewater treatment processes call for reliable real-time measurements to ensure a high level of diagnostics and control.

Ongoing Research

The past year has been marked by many other scientific advances supporting environmental protection and clean manufacturing. For example, the biocatalyst stability of a two-phase bioreactor system has been improved, increasing the process yield and optimizing bioproduct recovery. This system has a definite edge for the production of hydrophobic compounds. Work on remediating sites contaminated with energetic chemicals has resulted in the isolation of a new bacterial species, *Shewanella sediminis*. This bacterium, found in marine sediments in Halifax harbour, shows a natural capacity for *in situ* mitigation of RDX. As part of a project to optimize bioprocesses for the degradation of organic pollutants, a methanogenic/methanotrophic coupling approach has been developed for the *in situ* treatment of waters contaminated with chlorinated solvents. This co-metabolic conversion process is very cost effective.

Industrial Affairs

The Industrial Affairs's experienced personnel work closely with biotechnology and pharmaceutical firms, universities and other government departments—at local and international levels—to offer these organisms a wide range of business opportunities such as collaborative agreements, technology transfer, partnerships and fee for services. The flexible conditions we offer, combined with our researchers' expertise, represent an important asset and help these organizations to expand their research activities rapidly, without increasing their infrastructure and operating expenses.

Business Interactions

In 2004-2005, the Industrial Affairs Sector signed new collaborative agreements which have a total value of $3.3M and which span several years. These new agreements mean that NRC-BRI now has 56 active collaborative arrangements, up slightly from 2003-2004. Some of these 2004-2005 significant collaborative agreements are listed below.

- Ecotoxicology study of a defined portion of the St. Lawrence River, undertaken in collaboration with the Department of National Defence;
- Collaborative undertaking with a European institute, resulting in the identification of a family of genes found in *Micobacterium austroafricanum,* which participates in the biodegradation of Methyl Tertiary Butyl Ether (MTBE); efforts are under way to obtain a patent on these genes;
- Collaborative work with a European company to develop a production process for a therapeutic molecule; a licensing option is in the works for a stable clone of the patented 293ST-3F6 cell line;

- Collaborative arrangement with the *Université de Montréal* to broaden access to the services of the crystallography laboratory and the XB-C synchrotron laser and to adapt them for multiwavelength anomalous dispersion measurement;

- Development of anticancer therapeutics in collaboration with a young Canadian firm, and modulation of the kinetic properties of its technology platform;

- Collaboration with a Canadian company on the development of an industrial process for generating small interfering RNAs (siRNAs); this project could generate major spinoffs for the production of novel therapeutics.

In addition to these major contracts, some 100 contractual agreements totalling $1.5M have been signed with more than 50 organizations.

Technology Transfer Activities

In 2004-2005, seven new technology licences were granted.

- A licence for the "Novel Coumarin On/Off Switching Gene Expression System" has been granted to a large pharmaceutical firm working in the reagents field. This technology represents an efficient tool for inducible protein expression.

- A licence for the "Production of siRNA" technology has been granted to a biotechnology firm involved in the production of novel therapeutic molecules. This technology is designed to facilitate the production of novel therapeutic molecules using small interfering RNAs.

- Five new licences for the "pTT Vectors" technology have been granted to large pharmaceutical firms, bringing to 11 the total number of licences issued for this technology. This is an efficient, more economical system for transient transfection and recombinant protein production, allowing higher yields to be attained in the production of novel therapeutic tools at laboratory scale.

Networking and Partnerships

In October 2004, NRC–BRI and Laborium™, a Quebec start-up company in search of funding, concluded a strategic alliance to jointly offer various complementary services for manufacturing and packaging clinical lots of biological compounds according to good manufacturing practices (GMP or cGMP). This partnership also includes the establishment of a specialized training profile as well as a joint R&D program for developing and improving biomanufacturing methods.

In November 2004, NRC–BRI, signed a partnership agreement with McGill University and John Abbott College to establish an integrated cGMP-compatible bioprocessing/biomanufacturing program. This innovative partnership, a first between a university, a college and a federal research centre, could help to streamline training for technicians at the college level, for professional engineers at the university level and for industry professionals. The consortium is seeking funding for this innovative program.

These partnerships are a good fit with NRC-BRI's strategic project to create an integrated cGMP biomanufacturing and training centre. The aim is to cover the entire value-added chain of biopharmaceutical manufacturing effectively and to integrate practical elements into the training for employees specializing in this area.

The active search for funding and other partnerships will continue with a view to consolidating this strategic cGMP biomanufacturing initiative centred in Metropolitan Montreal. We have every hope that over the next few years the region will be able to position itself as a leader in cGMP biomanufacturing among the world's biotechnology poles.

Patents

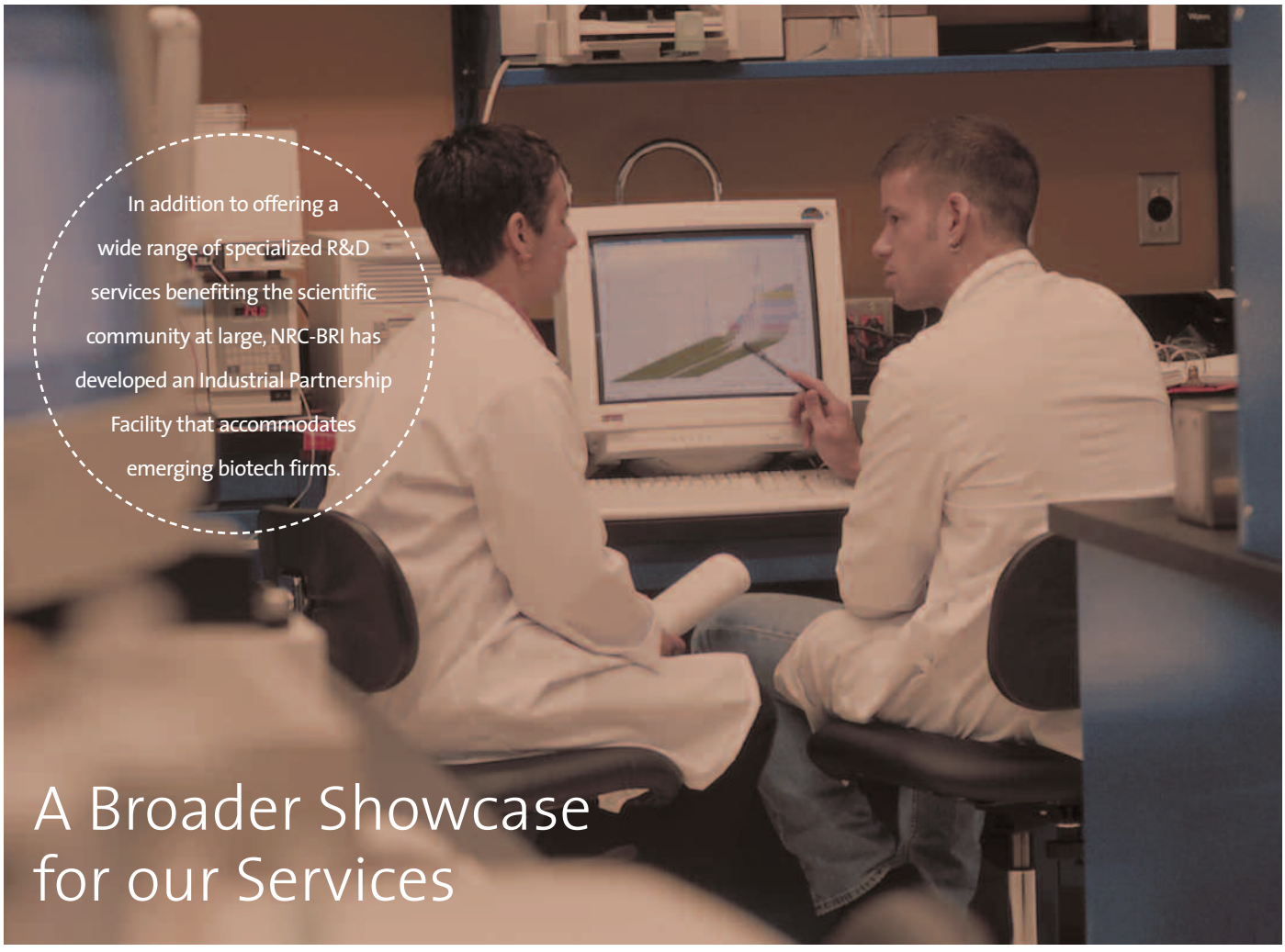
NRC-BRI is working on a bank of technologies and prospective products that hold promise for industrial applications. This year, the Institute reached cruising speed with some 30 patent applications being filed, adding to our existing portfolio of active patents for 54 protected technologies.

In addition, about 15 detailed evaluations of patents more than three years old have resulted in priority being assigned to four or five patents with a view to maintaining the protection they provide. One example is the maintenance of a patent on a therapeutic agent for treating diabetes-induced blindness. Various companies expressed an interest in these prioritized patents but they deemed the development too upstream and the commercial risk too high. Efforts will be devoted to deriving value from these technologies and prospective products within the Institute, while maintaining close ties with the private sector to encourage technology transfer in the future.

Marketing and Communications

To increase our visibility for business clients, the Industrial Affairs team has completely revamped the NRC-BRI Web site. With new features and a greater focus on business development, this site is now easier to get around in, and our services and technology transfer opportunities have been highlighted to a greater extent. One new feature is a Services section that directs users to the different service units at NRC-BRI. A dynamic database and a search engine help assist users in locating the latest information on the Institute's publications and patents.

NRC-BRI's Web site can be visited at www.bri-irb.nrc-cnrc.gc.ca



A Broader Showcase for our Services

Biotechnology, a rapidly expanding field in Canada, holds considerable potential for improving the quality of life of Canadians and furthering the knowledge-based economy. The NRC's Biotechnology Research Institute, a key player in promoting, assisting and integrating one of the largest and most dynamic biotechnology clusters in North America, has responsibility for stimulating and supporting the Canadian biotechnology community. In addition to offering a wide range of specialized R&D services benefiting the scientific community at large, NRC-BRI has developed an Industrial Partnership Facility that accommodates emerging biotech firms.

Specialized R&D Services

The NRC's Biotechnology Research Institute offers the scientific community a wide range of specialized R&D services in the health, bioprocessing and environmental fields. These technology platforms harness the expertise and skills of the Institute's researchers and employees as well as its state-of-the-art facilities.

NRC-BRI's turnkey services constitute an invaluable resource for third-party clients from the public and private sectors who occasionally need access to cutting-edge equipment or technologies or the support of highly skilled personnel to complement their research efforts.

In 2004-2005, we adopted a more dynamic commercialization strategy that gives greater visibility to our services on the NRC-BRI Web site and that encompasses a wider range of services. BRI's existing services (microarrays, high-throughput screening and pilot plants for microbial fermentation and mammalian cell culture) are now complemented by five new services: custom antibodies, custom peptides, flow cytometry, microscopy and imaging and waste biotreatability.

In 2004-2005

The Flow Cytometry Facility has purchased and installed a new generation flow cytometer, the FACSAria, which offers increased sensitivity, speed and efficacy for cytometric analysis and cell sorting. This system provides acquisition rates of up to 70,000 events per second.

The Microarray Laboratory has completed a major capital investment spread over two years involving the acquisition of a Biomek FX, an automated workstation for liquid handling.

The Animal Cell Pilot Plant has completed its largest production run on behalf of an industrial partner, consisting of a total volume of 330 litres of mammal cell cultures. The plant has also scaled up (45 litres) the transient transfection process developed by the Animal Cell Technology group. Thanks to this breakthrough, three batches of recombinant proteins were successfully produced at the 45-litre scale for different companies.

The Waste Biotreatability Facility conducted a process characterization and preliminary assessment for a pulp and paper company grappling with serious effluent treatment problems. By acting on the NRC-BRI's recommendations, the company has reduced its pollution load substantially and boosted production, thereby decreasing its economic losses.

The Custom Antibody Facility has a new cell culture room with state-of-the-art equipment.

The Industrial Partnership Facility provides the companies an ideal working environment for accelerating their development processes, reducing their technology risk and achieving their corporate objectives.

Industrial Partnership Facility

The Biotechnology Research Institute's Industrial Partnership Facility (IPF) is a scientific complex that offers turnkey laboratory space and unique services to assist companies involved in biotechnology R&D. Like established firms, start-up companies therefore have access to high-quality leading-edge laboratories suited to their needs.

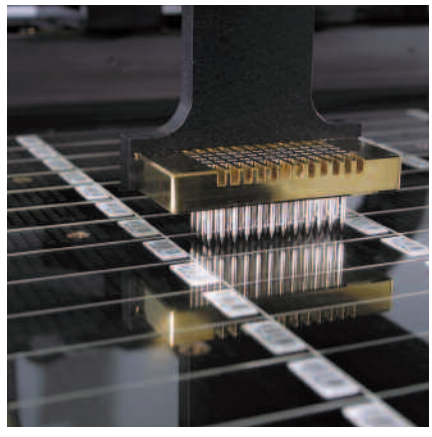
The IPF provides a unique environment for both young innovative companies and well-established firms and access to the expertise of NRC-BRI's researchers and its state-of-the-art facilities.

This strategically located facility promotes synergy by allowing the companies to establish cost-effective agreements with NRC-BRI's multidisciplinary teams and provides them with an ideal working environment for accelerating their development processes, reducing their technology risk and achieving their corporate objectives.

In 2004-2005

Once again this year the IPF has an occupancy rate of over 95%. A program of promotional activities has been developed and put in place to give greater visibility to its industrial services. Among other initiatives, the NRC-BRI's Web site has been revamped to provide a more comprehensive picture of the many services offered by the IPF.

We are proud to announce that two additional firms moved into the IPF this year: Advanomics Corporation and Ethanol Technology.



Finally, Biophage Pharma Inc. and the Biotechnology Research Institute have renewed their scientific collaboration agreement in the field of nanotechnology.

Fostering International Linkages between Science and Industry

The 10th annual *Crossroad of Biotechnology* conference was a resounding success. This event bearing the theme *Biomanufacturing: Innovative Bioprocessing Technologies and Strategies* brought together more than 135 organizations, including 100 private sector firms from 10 countries.

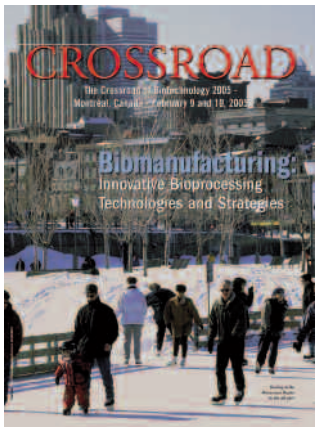
Every year, NRC-BRI employees organize large-scale events that capture a lot of attention.

Crossroad of Biotechnology 2005

The 10th annual *Crossroad of Biotechnology* symposium, held at the Biotechnology Research Institute on February 9 and 10, 2005, was a resounding success. This event bearing the theme *Biomanufacturing: Innovative Bioprocessing Technologies and Strategies* brought together more than 135 organizations, including 100 private sector firms from 10 countries. The participants praised the quality of the 2005 program, which brought together 26 speakers with biomanufacturing expertise from Canada, the United States, France, the Netherlands, the United Kingdom, Sweden and Switzerland. The exhibitors also seized the excellent networking opportunity that this event presented for their respective companies.

Presided over by J. Mark Lievonen, President of Sanofi Pasteur Ltd, the symposium profiled various trends in the biomanufacturing industry: production of new compounds at a lower cost, lack of production capacity in the industry, improvement in product characterization to meet the broader requirements of regulatory requirements.

The award dinner at this event provided an ideal opportunity to show that Montreal is one of the most dynamic biopharmaceutical clusters in North America. Alan DeSousa, who sits on the City of Montreal's Executive Committee and is also responsible for sustainable development, underscored this fact in his opening address by stating that Montreal is a life sciences research hub and it has all of the key components required for biotechnology: research and development, manufacturing and distribution. The 2005 edition of this international conference, which brought together hundreds of participants from the biopharmaceutical sector, helped to spotlight Montreal's successful positioning as a technology centre.



All those interested in following this major annual event linking science and business should visit the dedicated Web site at www.crossroadbiotech.ca.

Montreal Microarray Symposium

On March 17 and 18, 2005, NRC-BRI hosted the fourth annual Montreal Microarray Symposium, a key event that gives researchers in the microarray technology field a chance to get together to discuss new ideas, strategies and the most recent advances.

The excellent presentations by Dr. Michel Bergeron, Director of the Infectious Diseases Research Centre of Université Laval and by Dr. John Weinstein, Senior Principal Investigator at the National Cancer Institute at Bethesda, Maryland set the tone for the program, which this year featured 19 prominent speakers.

More than 350 participants from industry, government and academia took advantage of this opportunity to learn about the most recent advances in the microarray field. The topics covered included gene expression profiling, identification of targets for cancer detection, genetic diseases, genotyping, transcription factor networks, environmental monitoring, host-pathogen interactions and bioinformatics.

The tremendous success of this event has given excellent visibility to NRC-BRI and its microarray laboratory.

10th World Congress – Anerobic Digestion

The World Congress on Anaerobic Digestion was held in Canada for the first time last year. Organized by the NRC under the auspices of the International Water Association (IWA), the 10th annual congress was held in Montreal from August 29 to September 2, 2004.

Presided over by Serge Guiot, Group Leader, Environmental Bioengineering in BRI's Environment Sector, the 10th World Congress on Anaerobic Digestion brought together 523 delegates representing 52 countries. This phenomenal turnout, together with the large number of presentations (190), enabled the environmental experts in attendance to discuss fundamental principles and issues related to the application and promotion of anaerobic bioconversion processes.

In light of the growing government interest in sustainable development, the future of the anaerobic digestion process seems assured.

5th National Research Council's Genomics and Health Initiative Annual General Meeting

From May 16 to May 19, 2004, NRC-BRI hosted the NRC's 5th Genomics and Health Initiative (GHI) Annual General Meeting. The Genomics and Health Initiative (GHI) was launched in 1999 in order to bring the benefits of revolutionary advances in the genome sciences and health research to a variety of Canadian industrial sectors and regions. These advances are being achieved thanks to the NRC's expertise in its biotechnology research institutes, as well as the regional innovation networks across the country.

Presided over by Peter Hackett, then Vice-President Research, Life Sciences and Information Technology at NRC, the GHI May 2004 Annual General Meeting gathered some 215 participants who attended scientific presentations addressing the following themes: targets/therapies; application of proteomics technologies; microarray application; from the anatomical to the atomic of structures; and pathways and processes.

By merging the minds and talents of government actors, private industry and academia, GHI is bringing the life sciences sector to the forefront of the national and global scientific stage.

Our Researchers Share the Fruit of their Discoveries

NRC-BRI's scientific achievements give rise to a large number of articles published in prestigious journals. Some of these publications are listed below.

Health Sector

Lazar C, Kluczyk A, Kiyota T, Konishi Y (2004) Drug evolution concept in drug design: I. hybridization method. J. Med. Chem. 47: 6973-6982.

Lee CM, Nantel A, Jiang L, Whiteway M, Shen SH (2004) The serine/threonine protein phosphatase SIT4 modulates yeast-to-hypha morphogenesis and virulence in *Candida albicans*. Mol. Microbiol. 51: 691-709.

Harcus D, Nantel A, Marcil A, Rigby T, Whiteway M (2004) Transcription profiling of cyclic AMP signaling in *Candida albicans*. Mol. Biol. Cell. 15: 4490-4499.

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Michel G, Projasek K, Li Y, Sulea T, Linhardt RJ, Raman R, Prabhakar V, Sasisekharan R, Cygler M (2004) The structure of chondroitin B lyase complexed with glycosaminoglycan oligosaccharides unravels a calcium-dependent catalytic machinery. J. Biol. Chem. 279: 32882-32896.

Nagler DK, Kruger S, Kellner A, Ziomek E, Menard R, Buhtz P, Krams M, Roessner A, Kellner U (2004) Up-regulation of cathepsin X in prostate cancer and prostatic intraepithelial neoplasia. Prostate 60: 109-119.

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In 2004-2005, our researchers published 138 articles, 20 technical reports and 6 conference proceedings.

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Bioprocess Sector

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Hagedorn A, Levadoux W, Groleau D, Tartakovsky B (2004) Evaluation of multiwavelength culture fluorescence for monitoring the aroma compound 4-hydroxy-2(or 5)-ethyl-5(or 2)-methyl-3(2H)-furanone (HEMF) production. Biotechnol. Prog. 20: 361-367.

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Environment Sector

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Fournier D, Halasz A, Thiboutot S, Ampleman G, Manno D, Hawari J (2004) Biodegradation of octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX) by Phanerochaete chrysosporium: new insight into the degradation pathway. Environ. Sci. Technol. 38: 4130-4133.

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Lemarchand K, Masson L, Brousseau R (2004) Molecular biology and DNA microarray technology for microbial quality monitoring of water. Crit. Rev. Microbiol. 30: 145-172.

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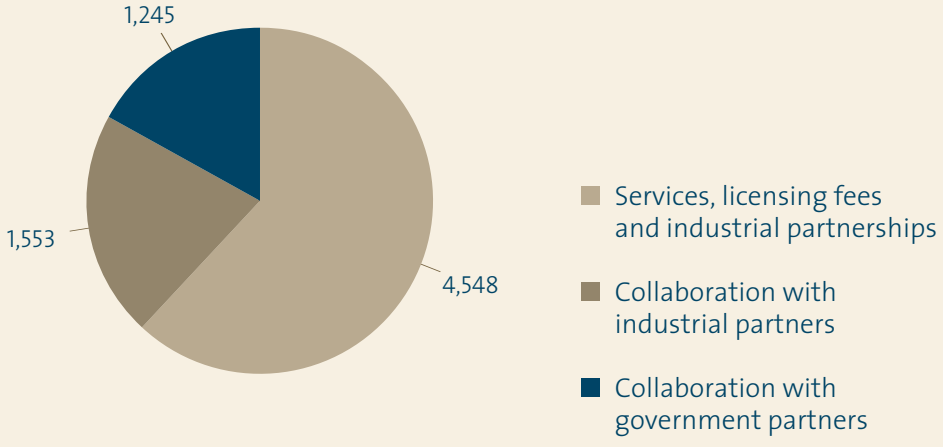
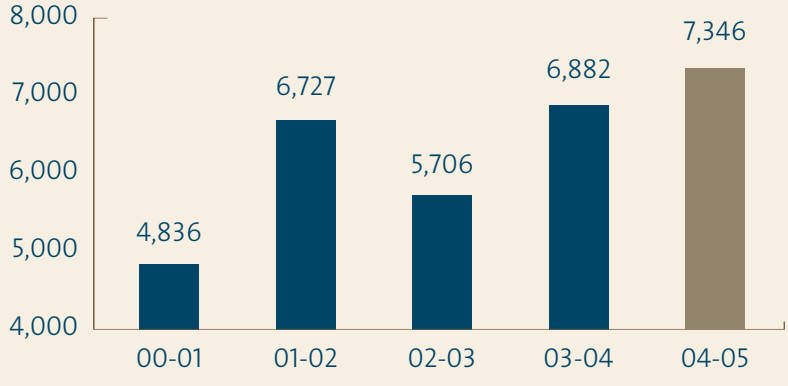
Financial Information for 2004-2005

Revenues

NRC-BRI Revenues in 2004-2005 (in thousands of dollars)



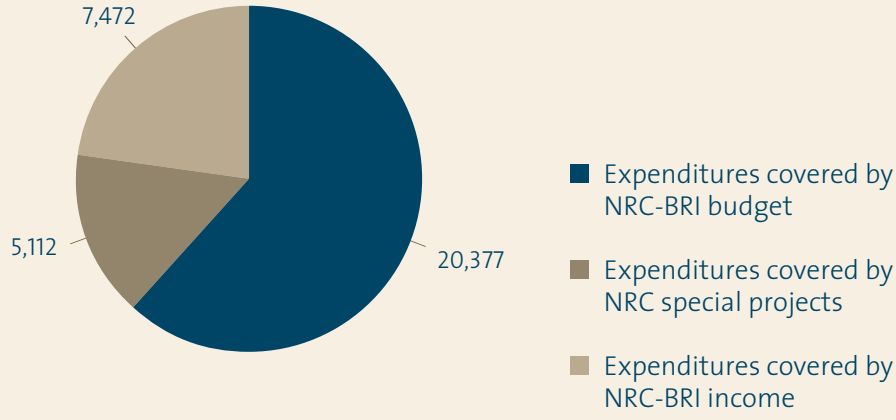
Change in NRC-BRI revenues (in thousands of dollars)



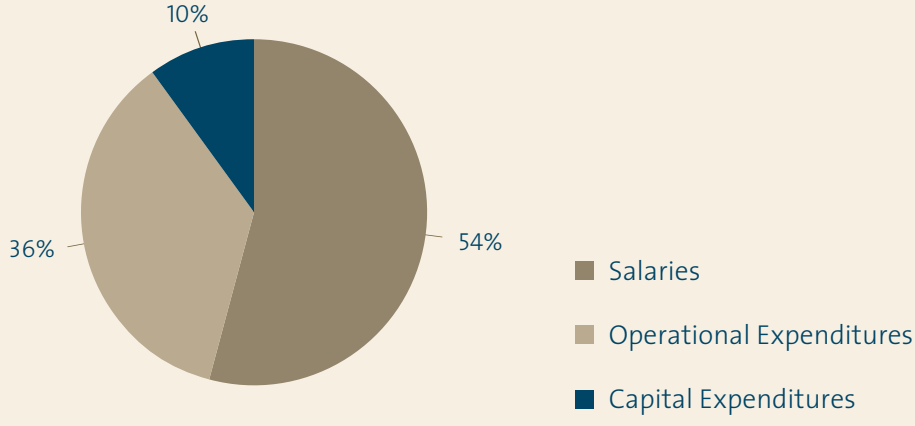
In 2004-2005, NRC-BRI posted its best performance in terms of total revenues since its inception. These revenues, which are comprised of service revenues and royalties from licensing, have enabled the Institute to offset the significant increases in its operating expenses.

Expenditures

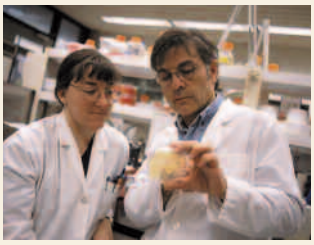
NRC-BRI Expenditures in 2004-2005 by Funding Source (in thousands of dollars)



Breakdown of NRC-BRI Expenditures in 2004-2005



NRC-BRI expenditures totalled $32,961,000 in 2004-2005. The breakdown by funding source is as follows: $20,377,000 from the Institute's budget; $7,472,000 from revenues earned during the current year and the previous year; and $5,112,000 from special NRC projects. In 2004-2005, the Institute's capital expenditures doubled from 5% to 10%, to meet the deadlines in its five-year plan.

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Andrew Storer, Ph.D.
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Biomolecular NMR and Protein Research
Characterize protein-protein interactions through the use of NMR and polypeptide engineering in order to support and guide advances in medical imaging and drug discovery.
Feng Ni, Ph.D.
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Chemical Biology
Development of novel methods of drug design and production and assessment of the therapeutic potential of these novel chemical compounds and their effects on biological processes associated with human diseases.
Yasuo Konishi, Ph.D.
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Computational Chemistry and Biology
Development and use of a wide variety of computational tools to create molecular models for characterizing protein-protein interactions at the atomic level; and design and optimization of therapeutic molecules.
Enrico Purisima, Ph.D.
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Enzymology
Identification and characterization of novel enzymes associated with cancer development and progression and with emerging infectious diseases, for potential target validation and drug development.
Robert Ménard, Ph.D.
Group Leader
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Genetics
Investigation of intracellular signalling pathways in order to characterize the events leading to cell survival, cancer or the development of infectious diseases and to design targeted therapeutic interventions.
Malcolm Whiteway, Ph.D.
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Macromolecular Structure
Determination of the structure of bacterial or mammalian proteins along with the structural characteristics of protein complexes using high-throughput methods; elucidation of their function, characterization of their mode of action at the molecular level and development of selective and potent inhibitors.
Mirek Cygler, Ph.D.
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Mammalian Cell Genetics
Development and use of novel molecular tools to identify and characterize the proteins of cellular machineries and of signalling networks that play a key role in the development of cancer or infectious diseases; and use of molecular tools and therapeutic agents to control or impede these processes.
Shi-Hsiang Shen, Ph.D.
Group Leader
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Receptors, Signaling and Proteomics
Elucidation of the molecular mechanisms underlying growth factor (EGF and TGF-ß) mediated tumourigenesis and development of linkages between molecular imaging/diagnostics and therapies based on inhibiting these signalling pathways.
Maureen O'Connor-McCourt, Ph.D.
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Bioprocess Sector

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Animal Cell Technology
Development and optimization of integrated bioprocesses using insect, mammalian or human cells for the large-scale production of therapeutic recombinant proteins, viral vectors and vaccines.
Yves Durocher, Ph.D.
Group Leader
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Microbial and Enzymatic Technology
Development, optimization and scale-up of bioprocesses using either micro-organisms or enzymes to produce chemical compounds or recombinant proteins.
Denis Groleau, Ph.D.
Group Leader
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Genomics and Gene Therapy Vectors
Design and development of effective and versatile expression systems and cell lines with a view to producing viruses (vaccines, gene therapy vectors), recombinant proteins and monoclonal antibodies for functional studies and therapeutic applications.
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Environment Sector

Adrien Pilon, M.Sc. Env.
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Environmental Genetics
Detection, identification and characterization of bacteria and viruses in samples from potentially contaminated sites to study the spread of and prevent diseases and devise ways of using micro-organisms and microbial diversity as environmental tools.
Roland Brousseau, Ph.D.
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Environmental Microbiology
Development and use of molecular techniques to isolate, quantify and monitor micro-organisms associated with the biodegradation of organic pollutants in soils, sediments and water and to analyse microbial diversity and response to environmental stresses.
Charles Greer, Ph.D.
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Environmental Bioengineering
Development of effective integrated technologies for treating wastewater and contaminated groundwater and for the conversion of organic wastes to bioenergy.
Serge Guiot, D.Sc.
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Environmental and Analytical Chemistry
Development and use of analytical tools for risk assessment and studying the fate of emerging contaminants and their degradation products in the environment; analysis and optimization of processes associated with biomass combustion.
Jalal Hawari, Ph.D.
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Biosensors and Nanobiotechnology
Development of innovative technologies for fabricating nanostructures with biological and electronics elements that can be used to detect pathogens, pollutants and biologically important molecules, in the environment, food, health and defence sectors.
John Luong, Ph.D.
Group Leader
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Bioconversion and Sustainable Development
Use of microbial diversity, genomics information and directed molecular evolution to identify novel bioreagents. Develop new sustainable biocatalytic systems for synthesizing new bioproducts and clean industrial bioprocesses.
Peter Lau, Ph.D.
Group Leader
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Applied Ecotoxicology
Development and conduct of ecotoxicology assays to assess, characterize and predict the effects of existing or new contaminants, such as chemical compounds, mixtures, bioproducts and bioprocesses, on key ecosystem components.
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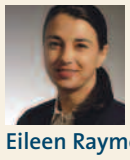
Industrial Affairs



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