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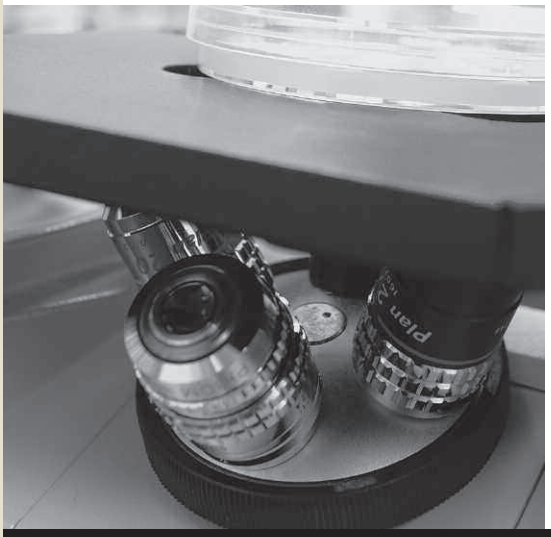
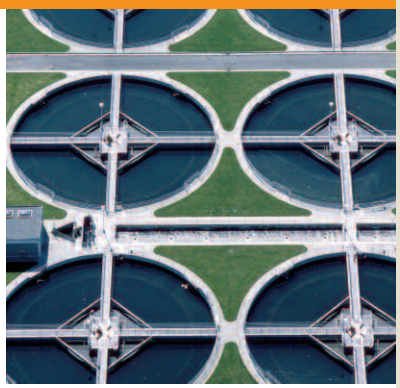
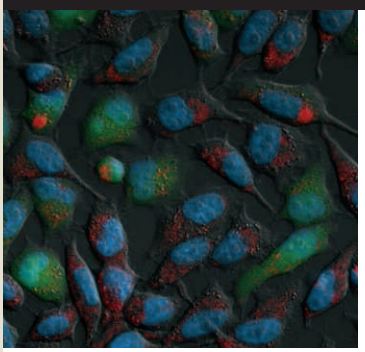
Biotechnology
Research Institute







nrc-bri
studying life

2005-2006 Activity Report

NRC Biotechnology Research Institute

National Research Council Canada
Conseil national de recherches Canada

Canada

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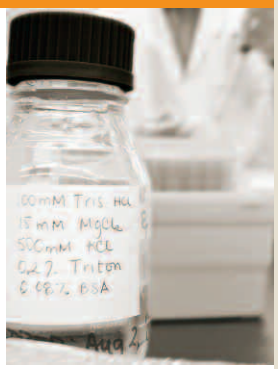
2005-2006 activity report



Optimization of recombinant gene expression in a methylotrophic bacterium Development of a new bacterial system for inducible, highly regulated gene expression in *Methylobacterium extorquens* through adaptation of elements from the *cym* and cumate operons of *P. putida F1.*

Efficient production of a gene therapy vector Development of a stable packaging cell line adapted to serum-free suspension culture that facilitates large-scale production of lentiviral vectors.

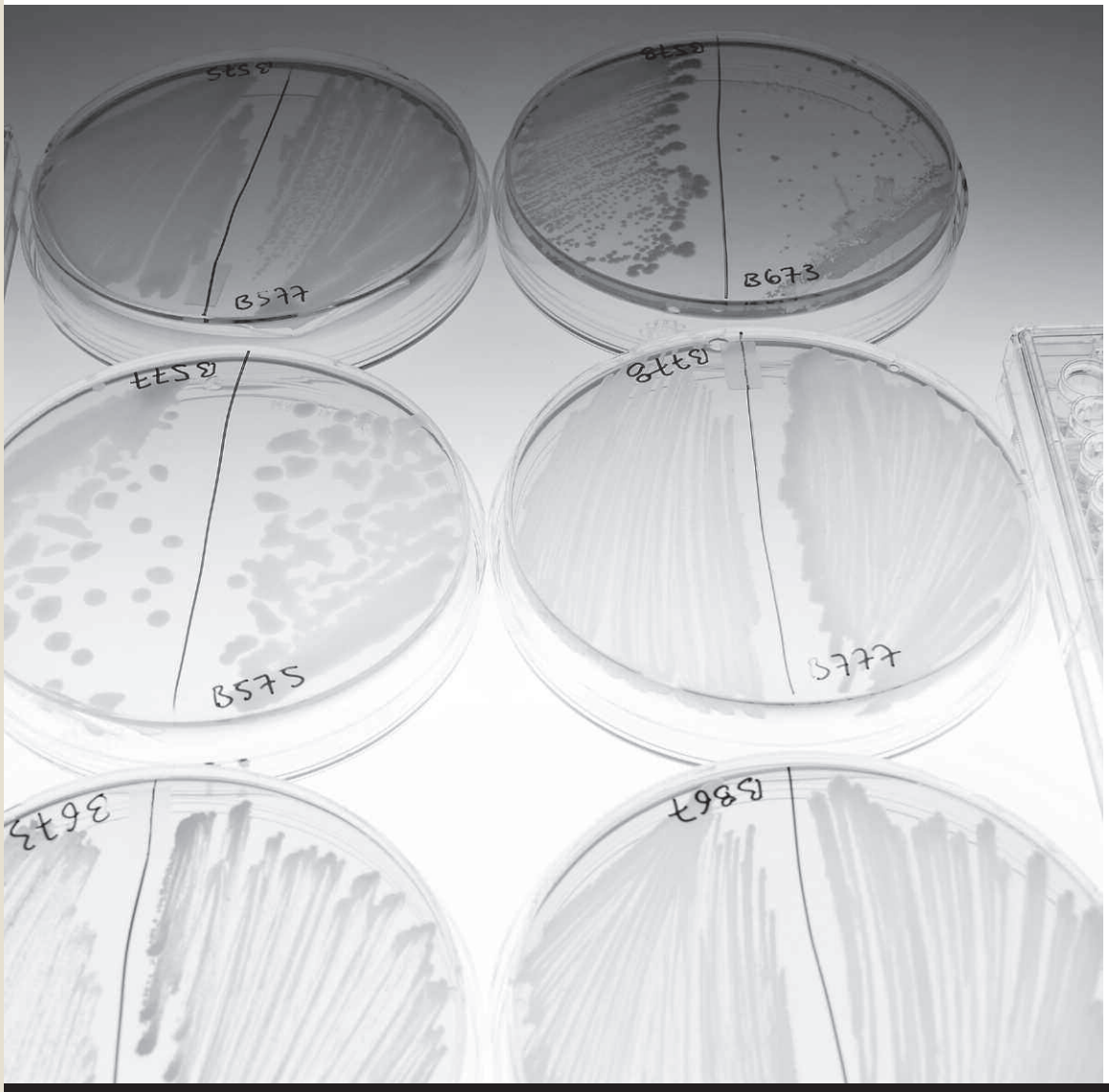
Isoproterenol to prevent cataract formation Demonstration of the potential activity of isoproterenol for preventing cataracts in the elderly, smokers and diabetics.

Controllable inhibitors for disease diagnosis and treatment Development of a new generation of powerful reversible inhibitors, controlled by the administration of an antidote, for the development of diagnostic and therapeutic applications such as anticoagulants.

New perspectives in the study of bacterial motility Characterization of the structure of an enzyme essential to the synthesis of flagella and presenting an interest as a therapeutic target to fight against major bacterial pathogens.

High-yield production of human interferon alpha in mammalian cells Development of a HEK293 cell clone that produces biologically active interferon alpha at high concentrations and a purification scheme yielding >90% pure Interferon.

Production of plastics from maple sap and syrup Development of a high-yield process for the bacterial transformation of sugars in sugar maple sap and syrup into biopolymers, without prior processing of these renewable resources.



Ultrasensitive microorganism detection method Development of a new class of nanobiosensors using electric cell-substrate impedance sensing (ECIS) for the speedy detection and identification of biological agents.

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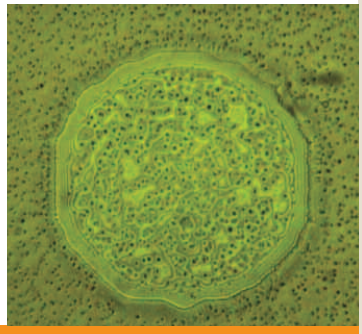
2005-2006 scientific highlights

Towards more effective biological degradation of explosives Identification and characterization of two new strains of *Shewanella* bacteria that can degrade explosives and possibly facilitate their elimination.

The Biotechnology Research Institute (BRI) of the National Research Council Canada (NRC) is the foremost facility dedicated to biotechnology research and development in Canada. In its nearly two decades of existence, the leading edge research at BRI has reflected the growing international impact of biotechnology and has earned the Institute a reputation for expertise and innovation in Canada and around the world. Its location in Montreal positions NRC-BRI as a central node within a North American hub for biotechnology and biopharmaceutical research.

Three sectors form NRC-BRI: the Health sector, representing BRI's largest research component, directs its efforts towards the research on cancer and infectious diseases, including drug discovery and development; the internationally renowned Bioprocess sector focuses on the development, optimization, and scaling-up of bioprocesses; and the Environment sector applies its expertise to two strategic areas: environment protection and clean manufacturing. Though most biotechnology research in Canada is currently dedicated to health care, environment-related research is expected to become more important, as sustainable development and climate change objectives warrant a shift towards greater efforts for the protection, cleaning, and monitoring of the environment.

Multidisciplinary research groups in all three sectors collaborate with industry partners as well as the larger research community (including universities and government agencies) in a variety of innovative research projects. NRC-BRI's cutting-edge infrastructures and state-of-the-art facilities (including the distinctive Industrial Partnership Facility) support the research activities of its scientists and engineers. Access to the Institute's specialized equipment, technologies, and expertise are also offered to partners and clients through research and service contracts as well as collaborative and technology transfer agreements.



nrc biotechnology research institute

Although Canadian biotech corporations have been facing capitalization problems with a decrease in their stock market valuation in 2005-06, the sector nonetheless posted a profit for the year. Not only did the publicly traded corporations reduce their losses, they saw their revenues rise over 25% to $2.5 billion.

The NRC's Biotechnology Research Institute has ridden the wave, recording revenues of over $8M in 2005-06, 18% higher than in 2004-05 and greater than anything it has seen since its inception. In total, the Institute has signed 28 co-operation agreements with public-and private-sector partners and nearly 120 contracts with over 90 organizations. What's more, the Institute welcomed two new tenants to its Industrial Partnership Facility: Viropro and Haemacure.

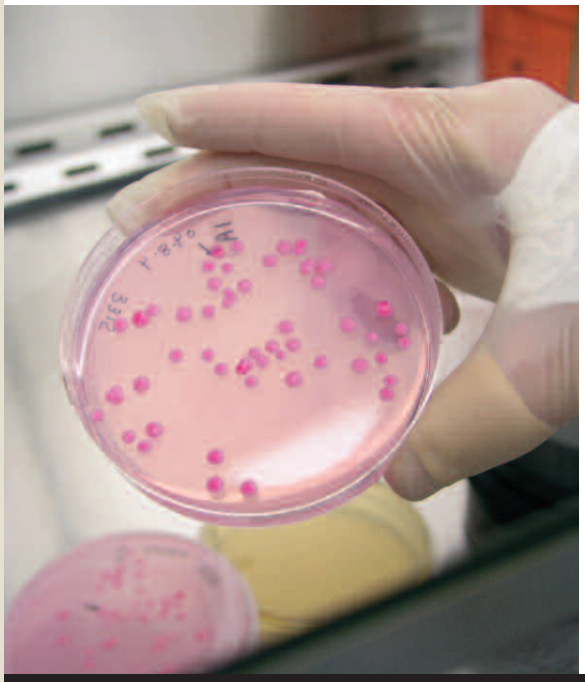
The 11th annual Crossroad of Biotechnology symposium held this year was dedicated to biotechnology and sustainable development. Chaired by Dr. Murray McLaughlin, the symposium drew nearly 300 participants from Canada, the United States and other countries.

In the area of intellectual property, the efforts of the past few years have had outstanding results: we have nearly doubled the number of our agreements under negotiation (35).

As far as science is concerned, we have made advances in our three main business lines, and our researchers have been recognized at the national and international levels for the quality of their work.

The NRC's strategic planning exercise continues, and we will be ready to take an active part in the activities the Council identifies as priorities for the coming years.

Michel J. Desrochers
Director General



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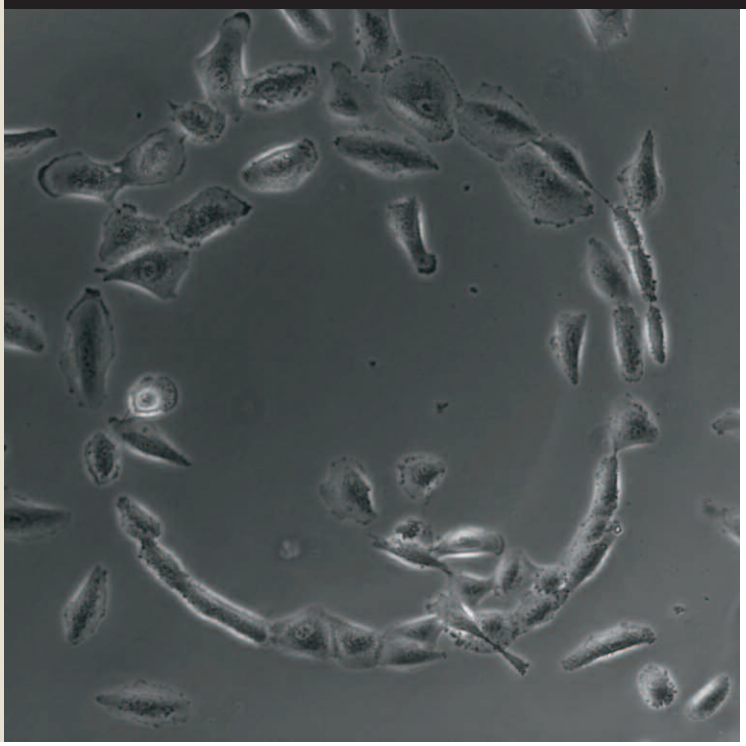
health sector



Based on current incidence rates, 38% of Canadian women and 44% of men will develop cancer during their lifetimes, and one out of every four Canadians will die from cancer. Worldwide, more than 17 million people die of premature deaths from infectious diseases, with most diseases classified as emerging or neglected. A key component of research at NRC-BRI is focused on the increasingly urgent areas of cancer and infectious diseases. The Health Sector's eight research groups use experimental approaches, including genomics, combinatorial chemistry, structural biology and bioinformatics, to identify and characterize molecular mechanisms of cancer, to enhance understanding of human pathogens, and achieve early drug development. In addition, the Sector is involved in the advancement of "enabling technologies", such as the development and application of computational tools for virtual screening, the study of signaling networks, and the design, synthesis and use of chemical libraries.

Major Advances

/ Smart molecules for drug discovery and targeted therapy The association of molecules is a basic phenomenon in most biological systems and many technological processes. While monovalency occurs when a ligand and a receptor associate by way of a single binding surface, multivalency is an extremely effective mechanism that confers a ligand the capacity to target multiple binding surfaces simultaneously through the specific and concomitant interactions of multiple binding domains. The ability to design and manipulate the constituent binding domains of multivalent molecular constructs for specific and retractable complexation of molecules is emerging as an increasingly successful strategy for research and therapeutic applications.

NRC-BRI scientists from the Biomolecular NMR and Protein Research Group have developed multivalent binding molecules containing linkers through which the association of biological molecules can be modulated. This approach was demonstrated through the design of a new generation of controllable anticoagulants. These inhibitors combine, in a single molecular structure, two independent binding moieties linked together by a flexible peptide bridge. Each binding moiety in isolation provided only moderate-to-weak binding affinity to thrombin; however, the resulting bivalent ligands have significantly increased affinity with values in the low- to sub-nanomolar range, typical of clinically successful thrombin inhibitors with anticoagulant activity.

The Group also showed that these potent thrombin inhibitors could be "switched" on and off by external triggers. Specifically, the Group demonstrated that the binding properties of two thrombin inhibitors could be controlled by the linkers binding to an SH_2 protein domain and an antibody, respectively. Since the linkers and the binding domains are, in principle, interchangeable, such an ability to modulate high-affinity binding paves the way for a number of practical applications in biotechnology and medicine. The desirability of such an approach is exemplified in the anti-cancer area, especially in the engineering of homing polypeptides for more effective diagnosis of cancer and targeted therapy. Multivalent polypeptides have the unique potential of being more selective to tumors or cancer cells within the inevitable background of healthy tissues often sharing similar molecular signatures.

/ Structure of an enzyme essential for the virulence of a pathogenic bacterium *Helicobacter pylori,* a major etiological agent of gastroduodenal disease, is a motile bacterium with significant medical and public health importance. Motility is a key virulence factor for this and other important pathogens, as it enables *H. pylori* to avoid the natural flow of the gastrointestinal tract and to colonize the gastric and intestinal mucosa. Flagella are the surface structures that provide the microorganism with the ability to be motile. Similarly to *Campylobacter jejuni, Helicobacter pylori* has been shown to modify the protein subunit of flagella, flagellin, with pseudaminic acid (Pse), a 9-carbon sugar that is structurally similar to sialic acid. Flagellar glycosylation has been implicated in immune avoidance, host/pathogen interactions, and the assembly and proper function of flagella. Consequently, the Pse biosynthetic pathway offers potential as a novel therapeutic target.

A key component of research at NRC-BRI is focused on the increasingly urgent areas of cancer and infectious diseases. The Health Sector's height research groups use experimental approaches to enhance understanding of human pathogens and achieve early drug development.

While the glycosylation of flagellin from a number of important bacterial pathogens has recently received considerable attention, the functional and structural characterization of the proteins involved in this process is still in its infancy. In collaboration with scientists from NRC's Institute for Biological Sciences, the Macromolecular Structure Group has determined crystal structures of the native PseC protein, an enzyme having aminotransferase activity that plays a central role in pseudaminic acid biosynthesis. This work presents, for the first time, a nucleotide-sugar aminotransferase co-crystallized with its natural ligand. These structures have allowed for the identification of key residues involved in the stabilization of the intermediate formed during the amino transfer reaction. Furthermore, the stereochemistry of the ligand bound in the PseC active site was determined and the essential role of a lysine in catalysis confirmed by site-directed mutagenesis. As a result of the increased resistance of bacteria to current antibiotics, new strategies to target these pathogens are urgently needed. One such strategy is to specifically target some of their key virulence determinants, including motility. As such, PseC provides a potential target for the fight against *H. pylori, C jejuni,* and a number of other significant bacterial pathogens, as it is essential for the assembly of functional flagellar filaments and consequent bacterial motility.

The Health Sector is involved in the advancement of "enabling technologies", such as the development and application of computational tools for virtual screening, the study of signaling networks, and the design, synthesis and use of chemical libraries.

/ Development of an eye drop against blindness Cataracts are the leading cause of blindness worldwide. Although diabetes is a major risk factor, the probability of developing cataracts increases greatly with age and smoking, even in the healthy, non-diabetic population. One of the major pathways implicated in the development of this disorder is protein glycation. This non-enzymatic binding of sugars to the body's proteins and nucleic acids (glycation) is a common biological phenomenon that increases with the existence of diabetes, smoking, and normal ageing. This process eventually leads to protein and nucleic acid degradation as well as increased oxidative stress, both of which play a large role in the development of cataracts, in addition to skin wrinkling, impaired muscle function, and brain degeneration. Although potent and safe inhibitors of protein glycation could offer a promising therapeutic approach for the prevention or treatment of cataracts, so far none of the agents investigated has proven clinically effective.

In the course of a drug repositioning program, the Chemical Biology Group screened compound libraries of existing drugs to identify new inhibitors of protein glycation. Among the compounds identified as having the activity was isoproterenol, an analog of epinephrine. One of the advantages of "drug repositioning" is the accumulated knowledge on existing drugs that results. For instance, isoproterenol is used as an inhaled aerosol to treat certain breathing and heart problems and is considered a safe agent for humans. It is also known to present high ocular absorbance and will not cause a reduction of intraocular pressure of the eye. Using a widely used diabetic rat model, the Group studied the effect of isoproterenol on the initiation and progression of cataracts. Its prodrug (D)-isoproterenol dipivalate hydrochloride was prepared in eye drop form and was applied to diabetic rats twice a day for up to 30 weeks. The effectiveness of (D)-isoproterenol was demonstrated, as it significantly delayed the initiation of the diabetic cataract in the rat model. This simple and innovative eye-drop product potentially offers a cost-effective alternative to surgery for the prevention and treatment of diabetes-, age-, and smoke-related blindness.

Ongoing Research

The year has been marked by many other scientific advances in cancer and infectious disease research. For example, a mutational analysis of a member of the quinate/shikimate 5-dehydrogenase family revealed an unexpected catalytic mechanism. Improved understanding of this important family of enzymes may prove useful in the development of novel herbicides and antimicrobial agents. In another research initiative, scientists demonstrated the important role of glycerol 3-phosphatase for osmoregulation in *Candida albicans*. Therefore, defects in glycerol homeostasis could have severe effects on the pathogenicity of this fungus and could serve as a future therapeutic target. In an effort to better understand the crucial role played by Transforming Growth Factor-beta (TGFß) in tumour suppression, a series of single amino acid TGFß type II receptor variants were generated and, three key residues were shown to contribute significantly to the differential affinity of the TGFß isoforms for this receptor. Using the known gene regulation data from *Escherichia coli* and computational analysis, scientists from the Sector found a common design principle for the transcription factors whose transcripts have short half-lives. Such mapping of the interactions between the thousands of genes of a cell is critical to defining and understanding normal and aberrant cell behaviour at the gene level.

A few publications of the Health Sector from 2005

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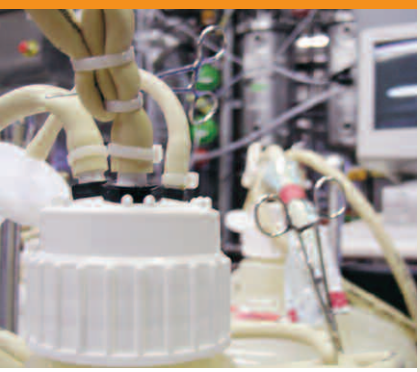

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bioprocess sector

Bioprocess technology is currently used in several fields of commercial biotechnology, and in the coming years is expected to have a wide spectrum of applications, from medical research and pharmaceuticals to food processing, agriculture, bioenergy and pollution control. The multidisciplinary research teams in NRC-BRI's internationally recognized Bioprocess Sector are engaged in a broad range of research activities for the development, optimization, and scaling-up of bioprocesses covering both upstream and downstream aspects. The Sector's scientists are highly experienced in vector design for gene therapy research, and the Sector also develops microbial, enzymatic, and advanced cell-based processes, which are then used by industrial partners for the production of valued biological and chemical compounds. NRC-BRI's state-of-the-art facilities allow for the large-scale industrial development of biopharmaceuticals and biologics, and its Bioprocessing Pilot Plant is now the largest of its kind in Canada.

Major Advances

/ *Methylobacterium extorquens* for controlled, high level expression of proteins The combination of recombinant DNA technology and large-scale culture processes has enabled the production of recombinant peptides and proteins in a number of hosts. Bacterial expression systems, whenever applicable, offer several advantages over processes based on the use of fungi or mammalian cells. For instance, bacteria are simple to manipulate, allow for the rapid production of recombinant proteins at a lower cost, and are easily amenable to high cell density fermentations. Still, none of the most popular expression systems are universally satisfactory. As a result, new expression systems are continuously under development to correct some of the deficiencies associated with current processes.

The Microbial & Enzymatic Technology Group has developed a new microbial expression platform capable of overexpressing heterologous proteins in high cell density fermentations. This platform uses as host a proprietary strain of the pink facultative methylotrophic bacterium *Methylobacterium extorquens*. Several elements and tools that permit efficient and cost-effective gene expression and recombinant protein production have been developed by the Group; these include novel cloning and expression vectors, transformation and mutagenesis protocols, and fermentation strategies. More recently, important additions to the *M. extorquens* expression toolbox were made by the Group, procedures for chromosomal gene integration were established, and an inducible and highly regulated gene expression system was developed. Practical and tightly regulated, inducible expression of recombinant genes in *M. extorquens* was attained by adapting the regulatory elements of the *Pseudomonas putida* F1 *cym* and cumate operons. This new tool—a cumate switch—allows for controlled expression of heterologous proteins and may become useful when attempting to express potentially difficult or toxic proteins to the host.

Through single and multicopy chromosome integration of heterologous DNA sequences, the Group also achieved stable and efficient high-level expression of recombinant proteins in the absence of antibiotic-based selective pressure. This is of particular interest for protein overproduction and green bioprocesses, where the use of antibiotics is not desirable. Due to the simplicity of the host's growth requirements, the inexpensive nature of its growth substrate, methanol, and the availability of genetic tools and procedures for efficient and large-scale recombinant protein production, this novel expression system possesses inherent economic and process advantages over alternate microbial expression systems.

/ Packaging cell line for the large-scale production of lentiviral vectors in serum-free suspension culture The transfer of genetic material is used for the treatment of a broad range of diseases through insertion of a functional gene into a cell in order to replace an absent or defective gene or fight an infectious agent or a tumour. Of the gene delivery systems, lentivirus-derived retroviral vectors hold substantial promise for gene therapy and other research applications, as they provide for the highly effective transfer of foreign genes and can direct their long-term stable expression. These vectors are also considered attractive gene transfer tools due to their biosafety and relatively large cloning capacity. However, the main

The multidisciplinary research teams in NRC-BRI's internationally recognized Bioprocess Sector are engaged in a broad range of activities for the development, optimization, and scaling-up of bioprocesses covering both upstream and downstream aspects.

advantage of lentivectors is their ability to incorporate heterologous genetic material into the genome of non-dividing cells such as neurons, macrophages, hematopoietic stem cells, myocytes, hepatocytes, and retinal photoreceptors. These long-lived cell types are predominant in the body and remain a desirable target of gene therapy for the treatment of chronic diseases, such as neurodegenerative, ocular, and cardiovascular diseases, and serious spinal cord injuries.

Progress is being made in developing lentiviral vector therapy, and encouraging preclinical data is accumulating. However, in light of the advantages associated with lentivirus gene delivery, there remains a need to improve large-scale production methods of clinical grade lentiviral vectors. Among the most important features are the use of media free of serum and animal or human proteins for increasing the safety of these therapy vectors and the ability to enhance vector yields. The Genomics and Gene Therapy Vectors group, in collaboration with the Animal Cell Technology group, has developed the first packaging cell line for the stable production of lentivectors in serum-free suspension culture. This packaging cell line has been engineered from serum-free adapted human embryonic kidney cells (HEK293) in order to produce high titres of conditional self inactivating (SIN) lentivirus vector. Among the stable clones obtained, some produced vector titres over $1X10E^7$ transducing unit/ml. Furthermore, the production of selected clones was observed for longer than 3 months in culture without selective pressure, thereby increasing the total recovery of lentiviral vectors by more than ten-fold in comparison with processes reliant on the transient production of recombinant lentiviruses. Owing to its stability and unique capacity for serum-free growth, this packaging cell line is of great value, as it allows for the efficient, high level production of lentiviral vectors without the need for any transfection, facilitates downstream processing operations, and meets the demands for clinical use in terms of safety, reproducibility, and standardization.

NRC-BRI's state-of-the-art facilities allow for the large-scale industrial development of biopharmaceuticals and biologics, and its Bioprocessing Pilot Plan is now the largest of its kind in Canada.

/ Production of a recombinant biogeneric drug with a human cell line Interferons are a group of natural proteins that are produced by cells in the body to help fight infections and tumours. Interferon alpha 2b (IFNα) belongs to the first generation of biopharmaceuticals derived from recombinant DNA technology, and it is still being used extensively in the treatment of various viral- and cancer-related diseases. With the patents for these first biotherapeutics now expiring, opportunities are emerging for the development of new processes that allow for the production of high value biogeneric products in a cost-effective manner.

IFNα is currently produced in *Escherichia coli* using a process that requires protein refolding and PEGylation, the latter of which is being used to increase protein half-life in the bloodstream, as no glycosylation occurs in this prokaryotic expression system. However, this chemical modification has the inconvenient effect of rendering IFNα less potent, leading to the need for higher doses in order to produce a therapeutic effect. Because they have all of the machinery necessary to allow for the comprehensive maturation of recombinant proteins, human cells are ideal hosts for the production of safe and effective protein drugs. In recent years, the NRC-BRI Animal Cell Technology group has developed a high yield and large-scale transfection platform for the rapid and scalable production of recombinant proteins in a human embryonic kidney (HEK293) cell line capable of growing in suspension and in serum-free medium. Using this platform, the Group has engineered a HEK293 cell clone that stably produces human IFNα at levels of 150 mg/L in an 8-day batch experiment. Furthermore, the Group has developed a purification scheme which yields >90% pure and biologically active IFNα. This high yield human cell-based integrated technology offers an alternative to current recombinant protein drug production processes, potentially allowing for the efficient and competitive biomanufacturing of new therapeutic candidates, such as a fully glycosylated IFNα biogeneric drug.

Ongoing Research

Research groups from the Bioprocess Sector have provided other advanced solutions in the development and optimization of processes and technology applications. For instance, heterologous extracellular production of a pediocin-like bacteriocin, Enterocin P, was successfully achieved using *Methylobacterium extorquens*. Such production of bacteriocins in safer heterologous hosts could allow their use as natural food antimicrobial agents. In an effort to enhance productivities of adenovirus vectors, metabolic flux analysis was applied to characterize the metabolism of 293 cells grown and infected in perfusion cultures. This analysis provided a rational basis for the implementation of a feeding strategy that allowed successful infection at a density of $5x10^6$ cells/ml. Collaborative research also led scientists from the Sector to gain better understanding of the genetic basis of susceptibility to *Candida albicans* infections. The study of mouse strains exhibiting different levels of resistance to systemic candidiasis allowed for the identification of complement component 5 gene as a major contributor to enhance susceptibility.

A few publications of the Bioprocess Sector from 2005

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environment sector

The coming years will bring to the forefront the need for science and technology solutions that can address such escalating environmental challenges as climate change, decreases in the quality and supply of freshwater, energy demand and alternative solutions, and sustainable industrial production. Using advanced biotechnology techniques, the Sector's scientists help to meet these challenges by creating processes and technology applications with the overreaching goal of reducing the environmental footprint of industrial activities and developing sustainable solutions and bioprocesses. The skill sets of the Sector range from unique expertise in bioremediation and biocatalyst development to the application of analytical chemistry, nanotechnology, DNA microarrays, and applied ecotoxicology. The seven research groups of the Environment Sector undertake solution-oriented research activities in two areas—environmental protection and clean manufacturing—and their work into environmentally friendly technologies engage all points on the industrial development continuum.

Major Advances

/ Nanobiosensors for high sensitivity microbial detection Nanobiotechnology couples biological elements and electronics to create powerful nanoscale biosensors that provide opportunities for the development of handheld analyzers for real-time, field, and point-of-care testing. With applications related to drug screening, clinical diagnostics, toxic substance monitoring in water, air, soil, and food, and the detection of biological warfare agents, nanobiosensors have far-reaching potential for making the world healthier, safer, and cleaner.

The Biosensors and Nanobiotechnology Group has developed, in collaboration with industrial partner Biophage Pharma Inc., a new class of nanobiosensors that use Electric Cell-Substrate Impedance Sensing (ECIS) for the rapid and simultaneous detection and identification of microorganisms in water, food, and biological fluids with greater sensitivity than existing technologies. The Group enhanced the impedance signal of the ECIS system through the development of a coating technology that allows the layering of cysteine over gold nanoparticles electrochemically deposited onto a gold electrode surface. The system was used to determine the presence of 15 different microorganisms (Biosafety levels 1 and 2). The system was also successfully applied to microbial detection in human serum and plasma samples.In addition, the impedance signal could be further enhanced by the use of a mediator couple such as ferro/ferricyanide which was very effective for the detection of *Escherichia coli,* such as the enterohemorrhagic strain designated *E. coli* O157:H7. Specificity of detection was achieved by a microbial-specific biocapture pretreatment step using magnetic iron particles carried out before the sample was added to the ECIS system. In all cases, the technology allowed a sensitivity level in the range of 5 cells per mL to be reached within 10–12 hours. These nanosensors constitute an important breakthrough in the speedy detection of living bacteria and will have wide applications in Biodefence, environmental monitoring, quality assurance of food and beverage, and biomedical diagnosis of antibiotic resistant bacterial infections.

/ Novel marine explosive-degrading bacteria Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) is widely used in the production of explosives and nuclear warheads. The manufacturing of this powerful and highly energetic chemical, as well as military activities such as land and sea testing and training, have resulted in severe contamination of some terrestrial and marine environments. Because this chemical contaminant is both highly toxic and responsible for causing adverse ecological effects, its removal from the environment is warranted.

In an effort to improve our limited knowledge on the fate and degradation of explosives in marine environments, the Environmental and Analytical Chemistry group found that indigenous bacteria from marine sediment obtained at a former ammunition dumping site located offshore of Halifax Harbour (Nova Scotia, Canada) could mineralize the explosive compound RDX. Characterization of this activity led to the isolation of several RDX-degrading bacteria with optimal growth temperature at 10°C to 15°C. These

The Environment Sector's scientists help to meet challenges by creating processes and technology applications with the overreaching goal of reducing the environmental footprint of industrial activities and developing sustainable solutions and bioprocesses.

isolates represent the first examples of psychrophilic marine bacteria with the ability to transform or degrade cyclic nitramines. Phylogenetic analysis indicated that some of these isolates fell within the genus *Shewanella*. Two of the bacterial strains belonging to the Na+-requiring group of *Shewanella* were analyzed further. Extensive phenotypic, chemotaxonomic, and genetic characterization revealed that both strains, HAW-EB3^T and HAW-EB4^T, were novel species, for which the names *Shewanella sediminis* sp. nov. and *Shewanella halifaxensis* sp. nov. were proposed, respectively. An upcoming genome sequencing project in collaboration with the US Department of Energy, the first of its kind for explosive degraders, will shed new light on the biochemical pathways by which these bacteria achieve *in situ* biodegradation and natural attenuation of these chemicals, thus helping to optimize bioremediation strategies for contaminated marine environments.

/ Bioconversion of maple sap into biopolymers Many consumer products, such as plastics, chemicals, lubricants, and fibres, can be made using biomass. This sustainable resource yields the carbohydrate feedstock used to manufacture biodegradable and environmentally friendly products. Maple sap and maple syrup, made by boiling and concentrating the sap, are examples of plant-derived biomass. With about 84% of the world's maple syrup production, the Canadian maple industry is exploring new options that can help producers increase the commercialization of their products.

The seven research groups of the Environment Sector undertake solution-oriented research activities in two areas—environmental protection and clean manufacturing—and their work into environmentally friendly technologies engage all points on the industrial development continuum.

The cultivation of maple tree sap has traditionally been geared towards the production of maple syrup. As part of an effort to explore the potential of maple sap and syrup for the development of high value-added bioproducts, the Analytical and Environmental Chemistry Group has developed a process to convert the constituents of this unique, natural, and renewable substrate into biopolymers. With sucrose in approximately 2% w/v concentration, maple sap provides an ideal carbon source for the production of biodegradable plastics such as polyhydroxyalkanoates (PHAs). Batch cultures of a bacterium known to accumulate a large amount of intracellular bioplastic PHA during growth on sucrose were investigated for producing polymer using maple sap as a sole carbon source. Maple sap was assimilated and successfully biotransformed into PHA. One key finding of the project was the discovery that maple sap yielded a relatively higher biomass and PHA content than pure sucrose-based media. Perhaps more importantly, the Group also found that no pretreatment prior to fermentation is required for maple sap, making the production of bioproducts from maple sap a cost-effective solution. This process will allow maple producers to benefit from additional income and thus, enhance income for the rural sector of Canada's economy. In using maple sap in the production of PHAs and other environmentally friendly products suitable for use in the health and food industries, sustainable development and industrial ecology guidelines will be upheld, and the maple industry will benefit from newfound opportunities.

Ongoing Research

Over the past year, scientists from the Environment Sector have contributed to other achievements in the areas of environmental protection and clean manufacturing. For example, an integrated aerobic and anaerobic system to remediate contaminated soil and groundwater was further optimized by the addition of a water electrolysis cell. The cell provides simultaneously and cost-effectively two essential ingredients, oxygen and hydrogen, and allows for faster and more complete degradation of chlorinated contaminants by this technology named "eMaMoC" (electrolytic methanotrophic/methanogenic coupling).

In collaboration with several NRC institutes and other companies and organizations, scientists from the Sector are applying their expertise to develop high value bioproducts that maximize the value of agricultural crop residues such as those from hemp

and flax. The novel applications stemming from this research will contribute to greenhouse gas reductions though the displacement of fossil fuels as a manufacturing feedstock and will contribute to the production of new biochemicals and biomaterials for industrial applications.

In an effort to improve the collection and processing of microbiological samples from permafrost and ground ice, novel methods were developed to monitor the penetration of exogenous contaminants during subsurface drilling. These quick and easy methodologies ensure maximum quality and reliability of data obtained on indigenous microorganisms and microbial communities, which could serve in the development of novel cold-adapted biotechnological applications.

A few publications of the Environment Sector from 2005

Bardai G, Sunahara GI, Spears PA, Martel M, Gong P, Hawari J (2005) Effects of Dietary Administration of CL-20 on the Japanese Quail (*Coturnix coturnix japonica*). Archives of Environmental Contamination and Toxicology, 49:215-222.

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Li CZ, Male KB, Hrapovic S, Luong JHT (2005) Fluorescence properties of gold nanorods and their application for DNA biosensing. Chemical Communications, 31:3924-3926.

Maynard C, Berthiaume F, Lemarchand K, Harel J, Payment P, Bayardelle P, Masson L, Brousseau R (2005) Waterborne pathogen detection by use of oligonucleotide-based microarrays. Applied and Environmental Microbiology, 71(12):8548-8557.

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Tartakovsky B, Manuel MF, Guiot SR (2005) Degradation of trichloroethylene in a coupled anaerobic-aerobic bioreactor: modeling and experiment. Biochemical Engineering Journal, 26(1):72-81.

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Zhao J, Manno D, Beaulieu C, Paquet L, Hawari J (2005) *Shewanella sediminis* sp. nov, a novel Na+ - requiring and hexahydro-1,3,5-trinitro-1,3,5-triazine-degrading bacterium from marine sediment. International Journal of Systematic and Evolutionary Microbiology (IJSEM), 55:1511-1520.

The Industrial Affairs team at NRC-BRI strives to create dynamic partnerships that link scientists and organizations with the wide range of services, cost-effective options, highly skilled personnel base, and state-of-the-art infrastructure available at the Institute. Local and international partners come from the academic, government, and private sectors to accelerate and maximize their research endeavors. The Industrial Affairs office works closely with each partner to find customized solutions that will incorporate the most appropriate services, including fee-for-service and technology licensing, to meet their business objectives.

Business Interactions

In 2005-2006, the Industrial Affairs Sector signed 28 new collaborative agreements with a total value of $8.9M—an increase of $5.6M compared to 2004-2005— which span several years. These new agreements bring to 43 the number of active collaborative agreements and include, among others, major work with:

- The Montreal Centre for Excellence in Brownfields Rehabilitation (MCEBR) to demonstrate the aquifer bioremediation by an electrolytic anaerobic/aerobic coupled biobarrier system.
- Natural Resources Canada to develop industrial uses for agriculture crop residues (fibres and shives), such as in composite materials for the automobile, aircraft and construction sectors, as well as to develop biochemicals as feedstock for the "green chemical" industry.
- Natural Resources Canada to develop bioprocesses for the conversion of industrial and municipal wastes into energy. The anticipated impact of this project is to demonstrate to industrial and public decision-makers that anaerobic digestion (AD) is a cost-effective solution when compared to incineration, landfilling or composting, with the additional cost-benefit of decreasing GHG emissions.
- Defence R&D Canada for the study of the degradation of energetic compounds contaminating the environment.
- The Department of National Defence for the development of a methodology and an evaluation program to ascertain the potential of adverse environmental effects from unexploded ordnance (UXO) and other contamination during UXO clearance of the Munitions Experimental Test Centre of the Lac St-Pierre Range.
- Merck Frosst for the scale-up and production of P450 cytochromes.
- The Lady Davis Institute, UQAM and Genome Québec for the validation of novel tumor markers and post-translational modified proteins in serum and other biological fluids of cancer patients.
- The Centre hospitalier universitaire de Québec and Genome Québec to develop novel rapid molecular theranostic technologies for the detection of nucleic acid.

In addition to these major collaborative agreements, some 120 contractual agreements totaling $3.8M have been signed with more than 90 organizations.

Technology Transfer Activities

In 2005-2006, twelve new technology licenses were granted.

- Six new licenses for the "pTT Vectors" technology that provides a cost-efficient system for transient transfection and high yield labscale production of recombinant proteins have been granted. This brings to 17 the total number of licences issued for this technology used as a tool in drug development and discovery programs.
- A licence agreement was signed with HyperOmics Farma Inc. for the commercialization of a range of selected monoclonal antibody (anti-GST) developed through the custom antibody Service of the Health Sector.

- The Environment Sector licensed two Multiwavelenght Fluorescence probes to Agropur. This technology represents an attractive option to single wavelength fluorescence in the development of online methods for bioprocess monitoring of Chemical Oxygen Demand (COD).
- Similarly, the bioprocess Sector licensed a Volatile Compound Extractor (VCE) probe to the agro food industry. This sterilizable probe allows a realtime monitoring of volatile compounds and their simultaneous extraction during the bioprocess. This technology improves the quality and the safety of productions generating volatile compounds by-products.
- A new Cumate-inducible switch was licensed to a biopharmaceutical partner. Our innovative molecular tool will most likely be used in the development of an expression system for specific protein production, in their cell based assays for functional genomics study and possibly to generate vectors intended to be used in gene therapy.
- The Downstream Processing Team of the Bioprocess Sector developed and assigned to its biopharamaceutical collaborator a new purification method for their high-value extracted protein.

Networking and Partnerships

In 2005-2006, NRC-BRI, in partnership with McGill University and John Abbott college, completed a detailed description for a new, integrated, cGMP-compatible bioprocessing/biomanufacturing program that would serve as a training centre for technicians at the college level, professional engineers at the university level, and industry professionals. This collaborative agreement would be the first to exist between a university, a college, and a federal research centre.

Patents

In 2005-2006, careful management of a portfolio containing 71 active intellectual property (IP) files allowed NRC-BRI to keep patent expenditures close to 10% of the planned budget. In addition, about 15 detailed evaluations of patents have resulted in high-priority being assigned to about 10 technologies for development and technological transfer. Seventeen patent files were abandoned because of their weak value potential. The number of licenses in active negotiation (35) doubled over the previous year. This year also saw the development and implementation of an intranet IP database which not only allows to better manage NRC-BRI's patent portfolio but also permits internal electronic access to up to date information on the intellectual property portfolio as well as disclosure of issued patents through the NRC-BRI website.

Market Studies

In addition to 15 individual market studies spotlighting various technologies, the Industrial Affairs team produced six major market studies. These studies were conducted for six of the Institute's strategic projects, with two studies per sector. The terms of references were reviewed and improved, leading to a public call for submissions that represents a model for NRC.

Marketing and Communications

For the promotion of technological marketing, the Industrial Affairs Office developed a new format for displaying their licensing opportunities, allowing a maximum of one page to detail the applications, concept, features and benefits of those technologies. To date, about 20 companies have expressed their appreciation for the new format, which will be applied to NRC-BRI's patent portfolio and made available on the Web for those technologies already in the public domain.

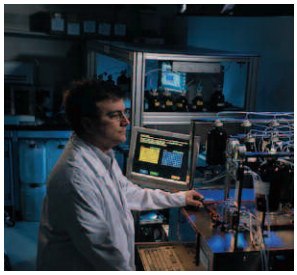
Also, there were a total of 10 delegations from 8 countries—Russia, Germany, the Netherlands, Belgium, Spain, Vietnam, Ecuador, and Columbia—visiting NRC-BRI's centre of operations in Montreal.

a step further in providing specialized r&d services

Through nearly two decades of existence, NRC-BRI has proven to be an effective catalyst for biotechnology and the strategic formation of regional clusters in Canada, thereby fulfilling one of the broader objectives of NRC by encouraging innovation and economic growth in the nation's communities. In Montreal, several initiatives have aimed at encouraging the city's standing as a "City of Knowledge"—a biotechnology cluster where leading-edge research is being conducted. With its critical mass of world-class scientists and research organizations, reinforced by the presence of several pharmaceutical industry giants, Montreal ranks as one of the world's leading centres in the rapidly evolving domain of life sciences. NRC-BRI works side-by-side with university, government, and private sector scientists to bring about discovery and commercialization in the fields of health, bioprocess, and environment. While NRC attracts first-rate scientists to the cluster, providing them with the state-of-the-art in equipment and infrastructure, BRI goes a step further by offering specialized R&D services, as well as space and equipment, to support scientific innovation, research partnerships, and opportunities to join forces with emerging or expanding biotech companies.

Specialized R&D Services

Because of the innumerable economic, health, and environmental benefits that can be gained through biotechnology, Canada must adapt a strategic position that will give precedence to the kind of biotech innovation that builds on Canada's already substantial strengths. In the latest wave of biotechnology-based innovation, key technologies such as genomics, proteomics, metabolomics, and bioprocess development will be expected to drive biological research for years to come.



NRC-BRI offers specialized services that further bear out its goal of championing innovation. Academic and industrial clients, in addition to partners, rapidly and easily gain access to the leading-edge processes, technologies, and expertise that support their R&D programs. At NRC-BRI, a vast range of technology platforms and scientific expertise are available on a fee-for-service basis, including high-throughput screening (HTS), microarray, microbial and mammalian cell pilot plants, flow cytometry, custom antibodies and peptides, microscopy and imaging, and waste biotreatability.

Over the past year, NRC-BRI has pursued its dynamic commercialization strategy by providing greater visibility to two new services on the NRC-BRI website: protein sequencing and mass spectrometry. Enhancements to the Services section of the NRC-BRI website are helping to ensure that interested parties may learn about the services offered and gain access to these services more quickly and easily.

/ In 2005—2006 The Waste Biotreatability Facility acquired a 1000L anaerobic digestor of CSTR type. This Continuously Stirred Tank Reactor (CSTR) enhances the capacity of the Facility to offer evaluation services in the areas of solid waste valorization and waste-to-energy conversion. Furthermore, a novel multi-wavelength fluorometer, developed in collaboration with the Envrionmental Bioengineering Group for on-line measurements of COD and VFA concentrations, has been installed at two wastewater treatment plants of a large agri-food producer. These systems enable early diagnosis of anaerobic reactor overload and feedback process control, resulting in improved water quality and reduced treatment costs.

NRC-BRI offers specialized R&D services, as well as space and equipment, to support scientific innovation, research partnerships, and opportunities to join forces with emerging or expanding biotech companies.

The Animal Cell Pilot Plant has completed several production runs of recombinant proteins with its HEK293 transient transfection platform. These production runs were jointly developed and optimized by the Facility and the Animal Cell Technology Group and carried out at the 45-litre scale for leading biotechnology and biopharmaceutical companies.

The Custom Antibody Facility has provided monoclonal and polyclonal antibodies to several internal and external clients and has signed a license agreement for its selected proprietary antibodies with HyperOmics Farma inc. Also actively involved in research supported by NRC's Genomic & Health Initiative, the Facility and NRC-BRI's Receptors, Signaling and Proteomics Group are developing antibodies for the treatment of cancer.

Finally, the NRC-BRI service facilities made substantial and recognized contributions in a number of scientific publications and presentations. Furthermore, their resources and expertise led to the presentation of several detailed technical reports to private sector clients.

Industrial Partnership Facility

The Industrial Partnership Facility (IPF) adds a valuable dimension to the Montreal biotechnology cluster by offering innovative technology-driven companies the chance to co-locate in a world-class research space. As a scientific complex offering turnkey laboratory modules to biotechnology companies, the IPF creates a stable environment in which to grow or expand. Partners benefit from collaboration: Private sector scientists can work side-by-side with NRC-BRI's scientists and draw on their globally recognized expertise for research and innovation. Partners also benefit from infrastructure: This business development facility provides industrial partners an unmatched opportunity to access NRC-BRI's state-of-the-art equipment and NRC's scientific and technical information resources and innovation assistance programs. Finally, partners benefit from synergy: Linking up with IPF introduces prospects for networking on a national and international scale by supporting public-private sector partnerships, allowing industrial partners to work jointly with the innovation capacity of NRC-BRI scientists, and helping to position Montreal as a hub for biotechnology research and commercialization.

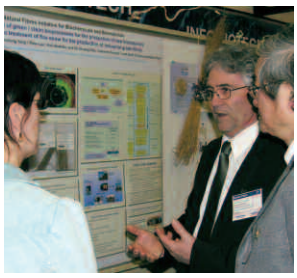
The IPF is home to a wide range of national and international firms involved in the identification of molecular targets for therapeutic applications, the offering of imaging services, the discovery, development, manufacture, and commercialization of ingredients for the distillery and fermentation industry, as well as products for the human and animal health markets worldwide.

/ In 2005—2006 Once again this year, the IPF maintained its high level of occupancy. Four companies successfully graduated out of the Facility, and thanks to its program of promotional activities, two additional firms have moved into the IPF: Viropro International, an expert in the production and set-up of technology transfers of therapeutic proteins, and Haemacure, a leading biomaterial company servicing the acute surgical wound care market.

The Industrial Partnership Facility (IPF) adds a valuable dimension to the Montréal biotechnology cluster by offering innovative technology-driven companies the chance to co-locate in a world-class research space.

Crossroad of Biotechnology 2006

The 11th annual BRI-hosted Crossroad of Biotechnology conference, entitled "Biotechnology and Industrial Sustainability", took place on March 22nd and 23rd, 2006, in Montreal. Once again, the conference was a great success. The high-quality programming drew 260 participants from six countries, and attendees included key industrial leaders, end-product clients and consumers, researchers developing new products, and industry stakeholders. Presided over by Dr. Murray McLaughlin, the conference took a practical approach, facilitating informative discussions on topics such as lowering greenhouse gas emissions, finding alternative energy sources for fossil energy, environmental testing, and designing enzymes and technologies that will support more sustainable and economically viable industrial processes; a sampling of success stories was also presented. The conference's theme and its status as an emerging field in science and industry provided a challenge for conference promoters, as many in the industrial sector are not aware of the pertinence and growing importance of biotechnology issues within the corporate environment. Fortunately, efforts at attracting business sector participants to the event helped to position NRC-BRI as an essential partner for Canadian industry and other federal departments in the undertaking of hard-hitting projects. The innovative format of the conference, characterized by its major partnership with the newspaper *Les Affaires,* provided a model of visibility for the future. All those interested in following this major annual event linking science and business should visit the dedicated Web site at www.crossroadbiotech.ca.

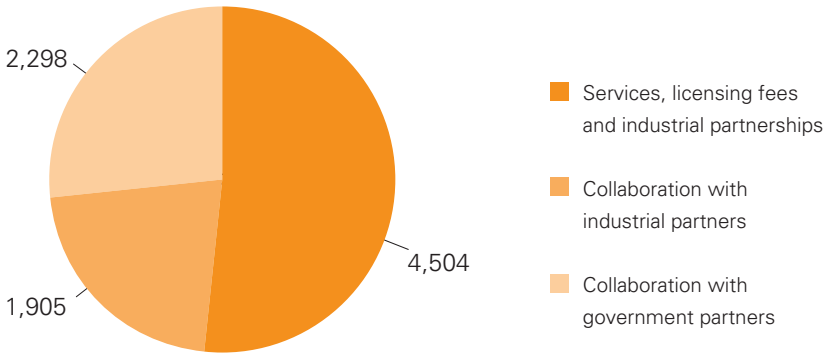


Apart from this major event, NRC-BRI scientists organized or sponsored a number of international conferences, workshops, and seminars this year, with 2 of them in the Bioprocess sector, 8 in the Environmental sector, and 4 in the Health sector. NRC-BRI scientists also participated in a number of international conferences, workshops, and seminars this year, with 7 of them in the Bioprocess sector, 22 in the Environmental sector, and 21 in the Health sector.

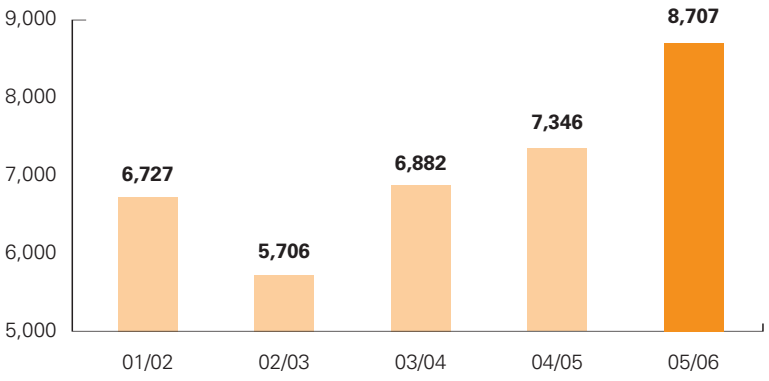
- The first place prize in the 2005 NRC Business Case Challenge, Technologies Available for Licensing was presented to Dr. Yasuo Konishi, the Group Leader of Chemical Biology, Health Sector, for the application of Isoproterenol as an anti-glycation agent.
- At a gala held during the Federal Contaminated Sites National Workshop, Dr. Charles Greer's team won a prize for Technical Innovation for their project on the *in-situ* treatment of sites contaminated by chlorinated solvents. The project was conducted in collaboration with Terrapex Environment, the Department of National Defence, and the Montreal Centre of Excellence in Brownfields Rehabilitation.
- Dr. Peter Lau received an award in recognition of Distinguished Services from the American Society for Microbiology.
- Last March, in the UK, NRC-BRI shared the 2005 TTP France Beaupre Award in recognition of its contributions to the environmental Key Technical Area (KTA) project initiated in 1998 by NRC-BRI and DRDC. The KTA working group, composed of international experts, aimed to determine the environmental fate and impact of energetic materials (EM), and developed an extensive protocol to characterize sites that have potentially been contaminated by explosives. An official website devoted to the protocol has been established (http://www.em-guidelines.org).
- The Institute was awarded two grants, totalling $1.8 million over three years, from the Canadian Biomass Innovation Network (CBIN). The mission of the CBIN is to coordinate federal research and development activities in bioenergy, biofuels, and industrial biotechnology and help the Canadian industry sector to meet efficiency, sustainability, and climate change goals. The "Natural Fibres Initiative for Biochemicals and Biomaterials" project, which will develop industrial uses for agriculture crop residues and develop biochemicals as feedstock for the 'green chemical' industry, was awarded a grant worth $1.4 million. The other grant, worth $0.4 million, was conferred for the project "Residual Organic Wastes to Bio-Energy", which seeks to develop bioprocesses for the conversion of industrial and municipal wastes into energy. This project is expected to demonstrate the cost benefits of anaerobic digestion as compared to incineration, landfilling, or composting.
- Beginning in 2002, NRC-BRI was at the centre of coordinated efforts by 43 scientists from 7 countries to determine the complete sequencing of *Candida albicans*. In June of 2005, the results were presented at the General Meeting of the American Society for Microbiology in Atlanta, and the following month, an article was published in the first issue of the American journal *PLoS Genetics,* revealing the complete genomic annotation.

Revenues

NRC-BRI Revenues in 2005-2006 (in thousands of dollars)



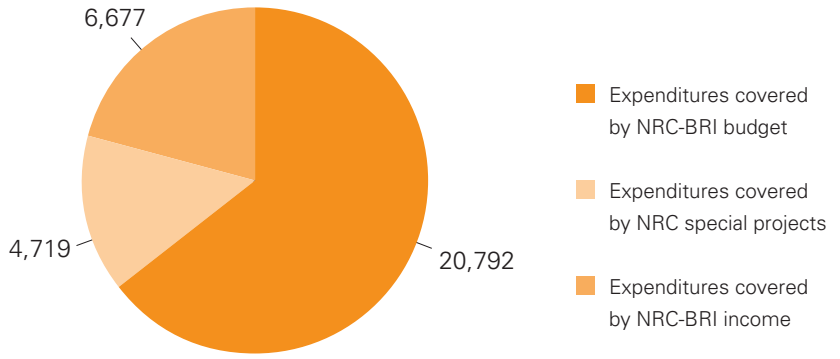
Change in NRC-BRI revenues (in thousands of dollars)



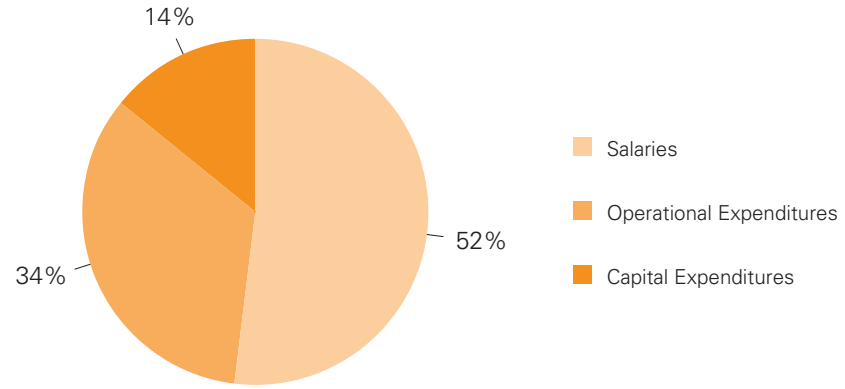
In 2005-2006, NRC-BRI generated a 18% increase in revenues compared to 2004-2005. These revenues, which are comprised of service revenues and royalties from licensing, have enabled the institute to offset the significant increases in its operating expenses.

Expenditures

NRC-BRI Expenditures in 2005-2006 by Funding Source
(in thousands of dollars)



Breakdown of NRC-BRI Expenditures in 2005-2006



NRC-BRI expenditures totalled $32,188,000 in 2005-2006. The breakdown by funding source is as follows: $20,792,000 from the Institute's budget; $6,677,000 from revenues earned during the current year and the previous year; and $4,719,000 from special NRC projects. Half of the capital expenditures are linked to the Institute's expansion and the other half to the purchasing of research equipment.

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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.

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Chemical Biology

Development of novel methods of drug design and production; assessment of the therapeutic potential of these novel chemical compounds and their effects on biological processes associated with human diseases.

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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; design and optimization of therapeutic molecules.

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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.

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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.

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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., Group Leader
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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; 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-,) mediated tumourigenesis and development of linkages between molecular imaging/diagnostics and therapies based on inhibiting these signalling pathways.

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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.

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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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Microbial and Enzymatic Technology

Development, optimization, and scale-up of bioprocesses using either micro-organisms or enzymes to produce chemical compounds or recombinant proteins.

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Environment Sector

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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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Bioconversion and Sustainable Development

Use of microbial diversity, genomics information, and directed molecular evolution to identify novel bioreagents. Development of new sustainable biocatalytic systems for synthesizing new bioproducts and clean industrial processes.

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Biosensors and Nanobiotechnology

Development of innovative technologies for fabricating nanostructures with biological and electronic elements that can be used to detect pathogens, pollutants, and biologically important molecules in the environment, food, health, and defence sectors.

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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.

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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., Group Leader
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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.

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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 responses to environmental stresses.

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