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The Canadian Regenerative Medicine and Nanomedicine Enterprise (CARMENE)

A framework for nanomedicine in Canada

In October of 2002, the Honorable Anne McLellan, Minister of Health endorsed the Bone and Joint Decade (2000–2010) on behalf of the Government of Canada, thus joining 45 countries, the World Health Organization (WHO), and more than 750 organizations and associations around the world. The goal of this global effort is to raise awareness and take action on bone and joint disease and injury, improve the quality of life for people with musculoskeletal disorders and injury throughout the world, empower patients to participate in their own care, promote cost-effective prevention and treatment, and advance understanding of musculoskeletal disorders through research to improve prevention and treatment. These include joint disease, osteoporosis, osteoarthritis, low back pain, spinal disorders, severe trauma to the extremities, and crippling disease and deformities in children. As our population ages, the prevalence of many chronic bone and joint diseases and conditions will continue to increase consuming a far greater proportion of Canada's health care resources. Chronic pain, loss of mobility and function, and loss of independence are common outcomes of a host of musculoskeletal and connective tissue conditions from osteoarthritis, systemic rheumatic diseases, osteoporosis and metabolic bone disorders to periodontal disease, fractures, and soft tissue injuries. The WHO estimates that several hundred million people already suffer from bone and joint disease and injuries around the world.

According to the Canadian Institutes of Health Research (CIHR) Institute of Musculoskeletal Health and Arthritis (May 2003), approximately 1.4 million Canadians are affected by osteoporosis, and this number is increasing as the population ages. By age 65 one in every two women will have osteoporosis, and by age 75, one in two will have experienced an osteoporotic fracture; and by age 90, one in three will have experienced a hip fracture (approximately twice the incidence rate in men). Women who have had an osteoporotic fracture are two to six times more likely to report difficulty in daily activities. Of those older people who experience a hip fracture, between 18% and 28% will die within a year of related complications. Total hip revision surgeries alone account for 25% of all implant surgeries after 15 years of implantation, or 30 000 surgeries in Canada. Such a limited lifetime may be appropriate for the elderly who might not live beyond this timeframe, but for an aging active baby-boomer generation, this will not suffice. Although Canadian bone research is at the forefront of science and technology, these grim statistics speak to the complexity of this formidable challenge and to the limited success of current therapies. Indeed, musculoskeletal diseases rank second among the four most costly illnesses in Canada at C\$17.8 billion/year (Arthroscopie 1998).

To outline the Canadian Regenerative Medicine and Nanomedicine Enterprise (CARMENE) (pronounced Carmen as in Georges Bizet's French opera). I will begin by defining nanomedicine and the focus areas of interest to the Canadian research laboratories. I will then briefly discuss the current federal and provincial funding for CARMENE before closing with a description of the growing opportunities for nanomedicine businesses in Canada.

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Nanotechnology and nanomedicine

Nanoscience and nanotechnology refer to research and development of technologies at the atomic, molecular, or macromolecular levels – research where the characteristic dimensions are less than 100 nm. Nanotechnology research provides a fundamental understanding of phenomena and materials that enable the creation and use of structures, devices, and systems which have novel properties and functions because of their extremely small size. Nanotechnology has the potential to change radically the study of basic biological mechanisms, as well as to improve significantly the prevention, detection, diagnosis, and treatment of diseases and adverse medical conditions. The key to this potential is that nanotechnology operates at the same scale as biological processes, offering an entirely unique vantage point from which to view and manipulate fundamental biological pathways and processes. For instance, bone is a nanostructured composite material made up mainly of collagen Type I (a triple helix 300 nm in length and 0.5 nm in width) and hydroxyapatite crystals (50 nm long and 5 nm wide) within which bone cells are housed along with a host of other macromolecules. These components of bone that house/ interface with bone cells are organized from nanostructures creating a familiar milieu for bone cell activity.

Recent advances in the understanding of, and in the ability to manipulate, matter at this scale have resulted in new opportunities for research and technological change in almost every field of science and engineering. For instance, recent studies from our groups and elsewhere have shown that nanoscale surface topography can influence protein adsorption and determine cell morphology and physiology, cell shape, spreading, and cellular function such as cell growth, differentiation, gene expression, or metabolism. Recent studies have shown that patterning of biomolecules in a self-assembled monolayer controls cell distribution, shape, and function most likely through the control of protein adhesion and cell behavior. It has become increasingly clear that bone cells do respond to nanofeatures but evidence for why and how they do so is still poorly documented. Nanotechnology provides the necessary tools at the required resolution for imaging, manipulation, and fabrication of nanofeatures similar to natural systems. It is thus possible, for instance, to systematically study and understand the mechanisms for bone cell response on nanostructured materials with tunable properties and architecture using both biochemical tools and physical techniques. An understanding of why and how cells respond to nanofeatures is very important in particular for the biomaterials and orthopedic communities because it offers new opportunities to engineer better implant surfaces

for improved cell- and tissue-material interaction, and better tissue engineered materials for targeted drug delivery in musculoskeletal tissue.

Nanomedicine is a multidisciplinary field of research, requiring expertise in, and integration of, engineering, science, and medicine, balanced with a consideration of the social, cultural, and ethical impacts of these novel technologies with key rehabilitation and accessibility issues, as well as the potential economic costs of such treatments. A turning point in the history of Canadian nanomedicine was reached when the Canadian Institutes of Health Research (CIHR) (<http://www.cihr-irsc.gc.ca>) and their partners (Canadian Space Agency, ALS Society of Canada, Canadian Stroke Network of Canada, Heart and Stroke Foundation, Jacob's Ladder, Juvenile Diabetes Research Foundation International, National Research Council of Canada, Natural Sciences and Engineering Research Council, NeuroScience Canada, Stem Cell Network, Ontario Neurotrauma Network) initiated the regenerative medicine and nanomedicine program in 2003 (<http://www.cihr-irsc.gc.ca/e/29542.html>). In this context nanomedicine was defined as the design, synthesis, or application of materials, devices, or technologies in the nanometer-scale for the basic understanding, diagnosis, and/or treatment of disease. The long-term goal of nanomedicine is to develop innovative and socially validated treatment approaches that will ultimately result in improved quality of life for afflicted individuals, populations, and their families. General areas of research currently pursued in Canada in this context include gene therapy, stem cell research, tissue engineering, and rehabilitation sciences. Specific applications of nanomedicine in Canada include (a) high resolution in-situ imaging, (b) nanoscale drug delivery systems, (c) ultrahigh-throughput multiplexed screening using nanodevices or nanostructured materials, (d) integration of nanodevices with microfluidic systems for application in sensing, (e) single molecule detection, function, dynamics, and reactivity, (f) nanosystems biology, (g) ethical, legal, cultural, and social consequences of nanomedicine, as well as the potential economic costs associated with it.

Funding nanotechnology in Canada

Since the implementation of the US national nanotechnology initiative with initial funding of over US\$400 million in 2000, annual spending in nanotechnology has now reached US\$750 million in Japan, US\$710 million in the US, US\$335 million in Europe, and US\$551 million in China, Korea, and Taiwan together. The Canadian government invested in education and research that resulted in major nanotechnology activities at most Canadian universities offering a PhD program in science

and engineering, nine institutes of the National Research Council of Canada (National Institute for Nanotechnology, Biotechnology Research Institute, Industrial Materials Institute, Steacie Institute for Molecular Studies, Institute for Microstructural Sciences, Institute for Aerospace Research, Integrated Manufacturing Technologies Institute, Institute for Fuel Cell Innovation, Institute for National Measurement Standards), and a nanotechnology funding envelop for university research and infrastructure programs through CIHR, NSERC (<http://www.nserc-crsng.gc.ca>), CFI (Canada Foundation for Innovation, <http://www.innovation.ca>), and the Canadian Institute for Advanced Research (CIAR, <http://www.ciar.ca>). Low cost tuition at major Canadian universities has created a highly educated talent pool. Funding for nanomedicine in particular was realized only recently through CIHR's regenerative medicine and nanomedicine initiative (see previous section). The last round of NSERC's Nano Innovation Platform Awards supported a good number of excellent, high-risk, high-gain projects in nanomedicine. At the provincial level, several initiative and networks are taking shape, such as the Advanced Systems Institute of British Columbia (<http://www.bcinnovationcouncil.com/>), or NanoQuébec (<http://www.nanoquebec.ca>) whose mission is to bring Québec to a leadership position in research and development of nanosciences and nanotechnologies nationally and internationally. The traditional provincial funding agencies such as the Alberta Energy Research Institute (AERI, <http://www.aeri.ab.ca/>) or the Alberta Agricultural Research Institute (AARI, <http://www.aari.ab.ca/>) also support nanomedicine-related project on a smaller scale. Overall, while funding is flowing into the Canadian research laboratories, there is still no national nanotechnology initiative to coordinate, track, and champion the cause of nanomedicine. The scientific community knows, and the Canadian government is aware, that to be a global player in nanomedicine, it is necessary to create and support national/provincial initiatives through competitive and organized provincial and federal funding. This is a unique opportunity, perhaps one of a kind in Canada, to shape the future of science and technology over the next few decades.

Nanotechnology business in Canada

To help take nanomedicine to the next level, it is necessary to develop high-value added products that outperform current state-of-the-art. For instance, implantable materials, targeted drug delivery systems, and early detection technologies for disease markers and pathogens, are anticipated to provide

the needed boost. Because of its vast wealth of natural resources, Canada is well positioned to be a major player in the commercialization of nanomedicine. Expertise, infrastructure, scientific environment, and technological clusters are key ingredient for the creation of nanobusinesses. Acceptance and integration of nanotechnologies particularly in nanomedicine will be a challenge for a number of reasons. Not only do they have to be approved by the regulatory agencies, but also their manufacturing may require significant technological and cultural adjustments on the part of the producers. According to the Canadian NanoBusiness Alliance (CNBA, <http://www.nanobusiness.ca/>), over 130 organizations are currently involved in nanotechnology in Canada. Virtually all activities are conducted in the vicinity of five nanotechnology hubs (Edmonton, Montreal, Ottawa, Toronto, Vancouver). Some of the nanotechnology applications currently pursued include real time, remote sensing systems for chemicals and pathogens, implantable medical devices, tissue engineering, and drug delivery systems.

Concluding notes

Finally, a few words about Bizet's legendary opera *Carmen*, which was premiered at the Opéra Comique de Paris on March 3, 1875. For a year after its premiere, it was considered a failure, denounced by critics as "immoral" and "superficial". Today, it is one of the world's most popular operas. In fact, OPERA America (<http://www.operaamerica.org/>) claims it to be the fourth most performed opera in North America. One may only hope that the fate of CARMENE will be that of *Carmen*. As is true for most paradigm-shifting research, it takes a few years for new ideas to take hold and for the research and development community to coalesce around those ideas and formulate thoughtful scientific plans. Nanoscale research has been percolating through the physical sciences and engineering communities for several years and has now reached the maturity to revolutionize medical research.

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