Skeletal Biology Research at the University of Western Ontario: Successful Synergy among Dental and Medical Scientists*

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Over the past 20 years, the School of Dentistry at the University of Western Ontario has fostered the development of oral health research. Dentists have partnered with colleagues in medicine and the basic biomedical sciences to establish the CIHR Group in Skeletal Development and Remodelling (**Fig. 1**), a world-class research group in skeletal biology that investigates the cellular and molecular mechanisms underlying the formation, destruction and tissue engineering of bone, teeth, cartilage and soft connective tissues. Knowledge obtained from these studies is crucial for understanding the pathogenesis, diagnosis and treatment of both musculoskeletal and dental diseases, such as osteoporosis, arthritis and periodontitis. In this article, we briefly review the history, current status and future goals of the group, with emphasis on the value of interdisciplinary teams comprising dental and medical scientists.

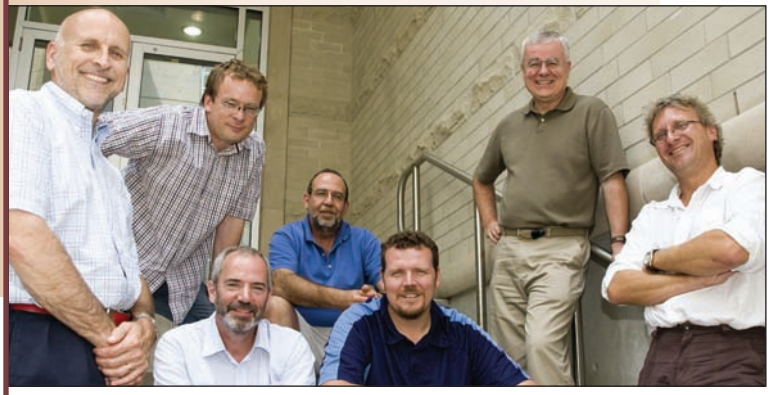

Figure 1: Principal investigators in the CIHR Group in Skeletal Development and Remodelling in 2008. From left: Drs. Stephen Sims, Andrew Leask, Graeme Hunter, Harvey Goldberg, Doug Hamilton, Jeff Dixon and Frank Beier.

Beginnings of Collaborative Work

In 1987, Dr. Jeff Dixon was recruited to the then faculty of dentistry at Western, supported by a 10-year development grant from the Medical Research Council of Canada. At that time, the faculty's main areas of research were orofacial pain and dental materials. In collaboration with Dr. Stephen Sims, who joined the department of physiology the same year, he began working on the biology of osteoclasts (**Fig. 2**). Drs. Sims and Dixon pioneered single-cell approaches to the study of osteoclasts, which permit tooth eruption and orthodontic movement of teeth through the jaw bones, as well as the destruction of bone in periodontitis and osteolytic tumours of the skeleton.[1]

A few years later, university funding became available for 2 full-time research positions, and the faculty of dentistry recruited Dr. Harvey Goldberg from the University of Toronto and Dr. Graeme Hunter from the University of Alberta. Drs. Goldberg and Hunter also quickly formed a productive collaboration, which led to the important discovery that bone sialoprotein — found in bone, dentin, cementum and calcified cartilage — nucleates hydroxyapatite crystallization.[2] They also identified osteopontin as an inhibitor of hydroxyapatite formation in soft tissues.[3]

By 1992, mineralized-tissue research at Western had achieved a critical mass. Drs. Dixon, Goldberg, Hunter and Sims established the Skeletal Biology Group, which became recognized as an area of research strength and priority. Additional funding from

**This article is dedicated to the memory of Dr. Suzanne M. Bernier, who passed away in 2007.*

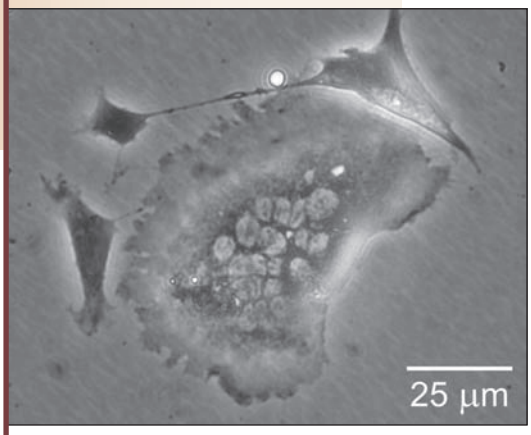

Figure 2: Single osteoclast (large cell) isolated from the bone marrow of a neonatal rat and visualized by phase-contrast microscopy; it contains approximately 20 nuclei and exhibits broad lamellipodia used for cell locomotion. Drs. Sims and Dixon seek to understand how osteoclasts are regulated and to develop new approaches for inhibiting the destruction of bone in periodontitis and rheumatoid arthritis.

the university allowed the faculty of dentistry to hire a molecular biologist, Dr. Michael Underhill, from Duke University, who established a strong research program on the genetic mechanisms underlying skeletal development. Musculoskeletal research was further strengthened in 1997 with the arrival of Dr. Suzanne Bernier in the department of anatomy and cell biology, funded by a competitive scholarship from the Arthritis Society. With postdoctoral training at the U.S. National Institute of Dental Research, Dr. Bernier brought to the group her expertise in cartilage and how it is broken down in arthritis.

At this point, the Skeletal Biology Group had become a successful multidisciplinary collaboration of researchers in the faculty of dentistry (Drs. Dixon, Goldberg, Hunter and Underhill) and faculty of medicine (Drs. Sims and Bernier). The merger of these faculties in 1998 validated the collaborative research enterprise and greatly facilitated further development of the group.

Funding and Facilities

In 2001–2002, several significant developments occurred. First, Dr. Frank Beier joined the department of physiology as a Canada Research Chair in Musculoskeletal Health. Dr. Beier, who acquired postdoctoral training at the University of Calgary, is an expert in the functional genomics of skeletal tissues.

Second, the researchers obtained a major grant from the Canadian Institutes of Health Research (CIHR), permitting establishment of the CIHR Group in Skeletal Development and Remodelling. CIHR's Groups Program funds teams of Canadian investigators undertaking collaborative research into critical health problems and, in this case, supports research training and core facilities at Western's School of Dentistry.

Third, 4 new laboratories were completed in Western's new Dental Sciences Addition building for the CIHR group, adjacent to existing oral biology and biomaterials research laboratories. Consolidation of the group within the Skeletal Biology Laboratories suite enhanced collaboration and provided an outstanding environment for training future scientists for both academia and industry.

Finally, the group spearheaded a successful funding application to the Canada Foundation for Innovation (CFI) for an integrated program in musculoskeletal research. The CFI is an independent corporation established by the Government of Canada to strengthen the capacity of Canadian universities, colleges and hospitals to carry out world-class research and technology development. With matching funds from the Ontario government, the university and industry partners, this grant provided $2.3 million for state-of-the-art research equipment and facilities.

Key Accomplishments

Thus, by the early 2000s, world-class personnel, space and equipment were all in place, allowing the CIHR group to make rapid scientific advances in a number of fields relevant to both medicine and dentistry, including the development of bone and cartilage, biomineralization and tissue destruction in inflammatory diseases such as periodontitis.

For example, with postdoctoral fellows Drs. Svetlana Komarova and Alexey Pereverzev and undergraduate dental student Jonathan Shum, Drs. Dixon and Sims solved the mystery of how acidosis leads to bone loss.[4] They examined the role of a protein called nuclear factor of activated T cells (NFAT) in mediating the effects of acid on osteoclasts and found that acidosis triggers a G protein-coupled receptor on osteoclasts. This leads to an increase in cytosolic calcium, which activates NFAT causing bone loss. These findings helped elucidate the biological basis of several diseases affecting bone, such as periodontitis, rheumatoid arthritis and the spread of cancer within the skeleton, and may lead to the develop-

ment of drugs that reduce pathologic bone loss, without disrupting normal bone remodelling.

In collaboration with Dr. Mikko Karttunen of the department of applied mathematics and graduate student Jason O'Young, Drs. Goldberg and Hunter pioneered the use of molecular dynamics in the study of biomineralization. Using supercomputers to simulate interactions between molecules, they were able to show that the crystal-inhibiting protein osteopontin uses both carboxylate and phosphate groups to form electrostatic bonds with calcium ions on crystal surfaces and prevent further growth of the crystal (**Fig. 3**). Used in combination with high-resolution microscopy, molecular dynamics[5] has tremendous potential to help us understand physiologic and pathologic biomineralization, including the formation of dental calculus and kidney stones.

Dr. Beier's laboratory uses gene arrays and genetically modified mouse models to examine the function of particular genes in the development of the skeleton and its destruction in osteoarthritis (**Fig. 4**). In collaboration with Dr. Bernier, Dr. Beier has discovered that the cytokine transforming growth factor α (TGFα) is dysregulated in osteoarthritis,[6] identifying it as a potential therapeutic target for the treatment of degenerative joint disease.

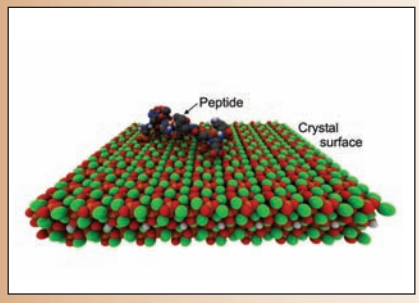

Figure 3: Drs. Goldberg and Hunter are studying the interaction of osteopontin with hydroxyapatite, the mineral component of teeth and bones. Molecular dynamics simulations, such as this one, provide insight into how this protein regulates crystal growth.

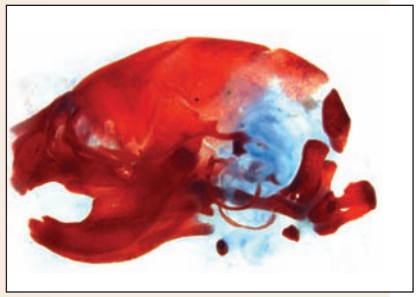

Figure 4: Staining of this skull from a newborn mouse shows bone in red and cartilage in blue. Dr. Beier and colleagues are examining the development of craniofacial structures in genetically modified mouse models.

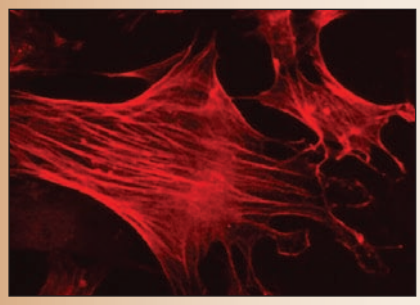

Figure 5: Microscopic image of fibroblasts isolated from a lesion in a patient with systemic sclerosis. Fluorescent labelling (red) reveals abundant α-smooth muscle actin in these cells, identifying them as myofibroblasts. Dr. Leask is seeking new therapies to prevent and treat fibrosis in systemic sclerosis and related diseases.

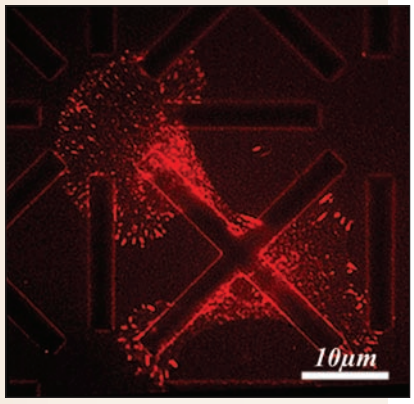

Figure 6: A rat osteoblast was cultured on a patterned titanium surface and stained with a red fluorescent label that reveals activated signalling proteins within the cell. Dr. Hamilton studies the way in which surface topography regulates the healing of tissues around implanted biomaterials.

Changes and Growth

In 2004, Dr. Underhill relocated to the University of British Columbia, while remaining a member of the CIHR Group in Skeletal Development and Remodelling. At Western, he was replaced by Dr. Andrew Leask from University College London in the United Kingdom. Dr. Leask's research program focuses on fibrosis — one of the largest groups of diseases for which there is no effective therapy. Systemic sclerosis can be fatal, as a result of heart, kidney, lung or intestinal fibrosis. Patients may also suffer from limited mouth opening, gastroesophageal reflux disease and xerostomia leading to severe oral disease.[7] Fibroblasts from tissues affected by systemic sclerosis produce excessive amounts of extracellular matrix proteins.[8] Dr. Leask has shown that these lesional fibroblasts express the highly contractile protein α-smooth muscle actin and thus are termed myofibroblasts (**Fig. 5**). In turn, the α-smooth muscle actin causes the fibroblasts to contract the extracellular matrix excessively, contributing to the fibrotic lesion. Dr. Leask's research suggests that drugs targeting the transforming growth factor-β and endothelin signalling pathways may be useful in combating this devastating disease.[9]

Before coming to Western, Dr. Leask worked in the biotech sector, providing him with expertise that is helping other group members transfer

their basic research findings into the corporate and clinical sectors.

Sadly, the group lost a founding member in 2007, when Dr. Bernier died of metastatic breast cancer. Her death deprived Canada's musculoskeletal research community of one of its most promising scientists and inspiring mentors.

In 2007, the group recruited Dr. Doug Hamilton, an expert in tissue engineering and biomaterials, who had carried out postdoctoral studies with Dr. Donald Brunette in the faculty of dentistry at the University of British Columbia. Dr. Hamilton's innovative studies address the mechanisms through which the surface topography of biomaterials influences the behaviour of host cells[10] (**Fig. 6**). This work has tremendous implications for understanding the responses of tissues to dental implants and is leading to the development of surface treatments that will speed healing and improve clinical outcomes.

A future goal of the group is to enhance the application of its basic research findings, in partnership with companies in the medical–dental devices, biotechnology and pharmaceutical sectors. Western's department of physiology and pharmacology recently recruited Dr. Cheryle Séguin from the Hospital for Sick Children in Toronto; her expertise in musculoskeletal tissue engineering and stem cell biology[11] will permit the "engineering" of skeletal and dental tissues. Such technology development will require the group's strengths in basic biology, along with complementary expertise in biomaterials provided by such other investigators in dentistry as Drs. Amin Rizkalla and Hiran Perinpanayagam (see articles in this issue of *JCDA* describing their current studies).

Current Status

The group currently comprises 63 people: 8 principal investigators, 2 visiting professors, 6 postdoctoral fellows, 20 graduate students, 15 undergraduate research trainees and 12 staff (**Fig. 7**). Principal investigators supervise research projects carried out by graduate students from a number of programs across the campus, including anatomy and cell biology, applied mathematics, biochemistry, biomedical engineering, developmental biology, orthodontics, physics and physiology. The group also trains students in the MD/PhD and Dental Clinician–Scientist Programs, which are aimed at preparing them for future careers in academic medicine and dentistry.

The group's research is supported by a total annual budget of $2.5 million from a number of external sources, including the CIHR, the Arthritis Society, Canadian Arthritis Network, Natural Sciences and Engineering Research Council of Canada and the Ontario Centres of Excellence. Group members also collaborate with several corporate partners in the pharmaceutical, biotechnology, medical–dental devices and instrumentation sectors. Integrated interdisciplinary research enables the group to make key discoveries and advance knowledge in ways simply not

Figure 7: Members of the CIHR Group in Skeletal Development and Remodelling, which brings together professors, postdoctoral fellows, graduate students, undergraduate research trainees and staff.

possible for individual scientists. The CIHR Group in Skeletal Development and Remodelling has transformed Schulich dentistry at Western into a leading centre for musculoskeletal and dental research (see www.cihrskeletal.ca).

Lessons Learned

What advice can we provide to other dental schools struggling to establish or maintain research groups in a highly competitive funding environment? Two key factors underlie the success of mineralized-tissue research at Western. The first is partnering with medicine and the basic biomedical sciences to establish a centre of excellence in an area of mutual interest. Such a strategy allows relatively small dental faculties to establish a critical mass of researchers from different disciplines to focus on a particular area of research, permits the effective sharing of resources and infrastructure, and allows the group to capitalize on the growing recognition of links between oral health and systemic diseases.

The second factor is strong support from the academic leadership at the department, faculty and university levels. The CIHR Group in Skeletal Development and Remodelling came into being only because deans Ralph Brooke, Robert McMurtry and Carol Herbert and directors Stanley Kogon and Harinder Sandhu shared our vision of researchers from different disciplines and academic units pooling abilities and resources to solve complex problems beyond the grasp of individual investigators.

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