Dr Alain Moreau provides an insight into his pioneering research that looks at the molecular genetics of musculoskeletal diseases with a focus on adolescent idiopathic scoliosis and osteoarthritis.

You are Vice Chair of the Institute of Musculoskeletal Health and Arthritis Advisory Board of the Canadian Institutes of Health Research (CIHR) and a leading research scientist in the field of molecular genetics of paediatric scoliosis. What are your current research foci?

Over the last 13 years, I have served in many leadership roles intersecting with research priorities and themes covered by the mandate of the Institute of Musculoskeletal Health and Arthritis. Although I am a biomedical scientist by training, those leadership and management positions helped me gain vast knowledge and vision in the musculoskeletal field: from oral health to paediatric and adult rehabilitation, from bench to bedside. My expertise ranges from basic biomedical to translational medicine, which is one of the strengths and attractions of my research programme.

How did you become involved in scoliosis studies?

Having recognised the lack of progress in the field of paediatric scoliosis, I was recruited in October 2000 by Dr Emile Levy – Director of Research at the Centre hospitalier universitaire Sainte-Justine (CHU Sainte-Justine) at that time – to establish a new laboratory to decipher the aetiopathogenesis of adolescent idiopathic scoliosis (AIS). AIS is one of the most common childhood deformities worldwide, characterised by a three-dimensional spinal deformity of unknown cause.

Unfortunately, today’s patients are treated in largely the same manner as those 30 years ago. Due to patient discomfort and risk, current treatments, including bracing or surgical correction, are delayed until significant deformity or progression is detected. This results in suboptimal treatment, significant psychological sequelae and heavy economic burdens for families. Therefore, earlier detection and better stratification of AIS patients are crucial to broaden the range of treatment options and increase effectiveness.

Supported by grants from CIHR, the Natural Sciences and Engineering Research Council of Canada, Fondation Yves Cotrel and Génome Québec, to what extent has such funding enabled the advancement of your research?

As a young faculty member, I was lucky to gain funding immediately from Fondation Yves Cotrel (Institut de France, Paris), which presented me with my first research grant as Principal Investigator through its international open competition programme. Indeed, I was the first Canadian scientist to be a laureate of this prestigious foundation and the only one in the world to receive this honour three consecutive times (2002, 2005 and 2008).

In recognition of my achievements in the field of scoliosis and my unique collaborative spirit, I was awarded the very first Medal of the Fondation Cotrel-Institut de France in November 2012. Indeed, the support of the Cotrel Foundation was instrumental to my career progression, awarding me more than CAD $1 million in the last decade – a world first for a scoliosis researcher!

I received instrumental support once again in 2005, when I met Marc Viscogliosi, CEO and Chairman of Paradigm Spine LLC and Fourth Dimension Spine LLC (New York, USA), who had the vision to support my translational research. In June 2006, Paradigm Spine LLC signed a patent license and sponsored an R&D agreement (which was transferred in 2012 to Fourth Dimension Spine) with CHU Sainte-Justine and I, obtaining an exclusive global license to commercially develop, produce, sell, distribute and sublicense patent rights and related technology. Over the last seven years, Paradigm Spine and Fourth Dimension Spine have jointly invested more than $10 million into my scoliosis research programme.

Could you provide an overview of Canadian medical efforts currently underway to advance the understanding of the genetic causes of osteoarthritis and scoliosis?

I have had the opportunity to visit many research centres, hospitals and universities across Canada, and I can assure you that Canadian researchers are leaders in the field of osteoarthritis and scoliosis.

With the support of CHU Sainte-Justine, as a researcher I have developed collaborative agreements with 10 major paediatric spine centres in Canada. This coast-to-coast national network is the first of its kind in Canada, and is part of my long-term commitment and mission to improve Canadian health by integrating all major national paediatric spine centres into a unique collaborative clinical and research network. This joint effort is unprecedented in the field of scoliosis and will serve to improve research in the field.

What are the major challenges to the development of prognostic methods for the early screening of AIS?

The major obstacle inhibiting the development of prognostic tests is the heterogeneous nature of AIS. At the clinical level, AIS heterogeneity is clearly illustrated by the variability of curve patterns, localisation and curve magnitude, even in families with multiple affected members. In the absence of reliable AIS phenotypes, my team and I have undertaken research to understand the molecular changes associated with disease onset and spinal deformity progression.

A molecular definition of disease is rapidly replacing traditional pathology-based disease descriptions, in part because of its utility in identifying the optimal treatment regimen for patients. Many common chronic diseases will...
MENTOR

Dr Alain Moreau introduces an unusual training programme funded by CIHR for young musculoskeletal health researchers

My laboratory is an international training platform where my staff and I are responsible for teaching and supervising technical staff in Milan and Hong Kong clinical trial sites as well as training graduate students from different programmes. Among others, the MENTOR training programme in musculoskeletal health was instrumental in the development of several multidisciplinary research teams in Montreal involving researchers from different research and teaching institutions. MENTOR requires that all trainees are supervised by two experts in order to broaden their training. This unique training programme has been very successful so far in enhancing our research capacity in the field of musculoskeletal health and preparing the next generation of young scientists in Canada.

benefit from this disease definition method and scoliosis is no exception. It is anticipated that a new continuum of care will emerge with the arrival of early scoliosis diagnostic and prognostic tests.

How has research into the molecular mechanisms implicated in inflammation and pain, and the normal and pathological regeneration of musculoskeletal tissues contributed to understanding of degenerative skeletal disorders?

We have made trailblazing discoveries regarding the role of specific biomarkers involved in adult and paediatric chronic diseases. Despite commonalities, little is known about the molecular mechanisms by which chronic inflammation is induced and sustained in many important human diseases. A clear understanding of network interactions between specific biomarkers and chronic diseases is valuable for the development of better drugs and drug combinations, and for better patient selection in order to reduce the side-effects associated with these treatments, increase therapeutic efficacy and offer new therapeutic options.
Musculoskeletal medicine

Researchers at the Centre hospitalier universitaire Sainte-Justine in Montreal, Canada are conducting pioneering work in the field of musculoskeletal diseases and developing cutting-edge predictive techniques for two conditions – scoliosis and osteoarthritis.

IN CANADA, MUSCULOSKELETAL (MSK) diseases affect 11 million people over the age of 12, often leading to incapacitating physical and functional limitations as well as psychological issues. Further to the burdensome impacts on quality of life, MSK diseases are a huge economic drain for the Canadian Government.

A particular challenge for the MSK disease research community is developing an effective treatment for adolescent idiopathic scoliosis (AIS), an inhibiting and lifelong chronic condition. Currently, 4 per cent of Canadian adolescents suffer from AIS, and one out of every six children diagnosed with the disease will have a progressive spinal curve that requires active treatment.

A PIONEERING PREDICTION

For the last 30 years, patients have endured painful treatments that do not necessarily lead to improvements in the condition; and to date, no therapies are offered for deformities of the spine between 10° and 25°. At that stage, the individual is simply kept under observation, as doctors wait for the deformity to progress to between 25° and 35° before recommending the use of external bracing. Patients are only admitted to surgery if their spinal curve exceeds 45°.

In response to slow progression in AIS treatment, researchers are currently striving to design and validate comprehensive prognostic techniques for paediatric scoliosis. Dr Alain Moreau – Vice Chair of the Institute of Musculoskeletal Health and Arthritis Advisory Board of the Canadian Institutes of Health Research (CIHR), Professor at the Université de Montréal and Director of the Viscogliosi Laboratory in Molecular Genetics of Musculoskeletal Diseases at the Centre hospitalier universitaire Sainte-Justine (CHU Sainte-Justine) – is a leading international expert on the molecular genetics of paediatric scoliosis.

A pioneer in the field, Moreau has developed a cutting-edge technique to determine the causes of scoliosis in children. His pivotal aetiological method was developed based on his observations of adolescent patients. Moreau identified a differential signalling dysfunction of specific Gi-coupled receptors, which allowed him to group AIS patients into three biological endophenotypes with a simple blood test: “Patients classified with the FG2 endophenotype are more susceptible to developing severe scoliosis, while those with the FG1 endophenotype present a much lower risk of disease progression,” Moreau elaborates. His research team further established that patients classified as part of the FG3 group were the most responsive to rigid bracing, which demonstrates that the these predictive methods can indeed pinpoint the likelihood of patient response to this form of treatment. Stratifying patients according to their endophenotypes should enable doctors to provide more effective, personalised care.

Moreau developed a second biochemical scoliosis blood test that measures osteopontin (OPN), a multifunctional secreted cytokine, and soluble CD44 (sCD44), a protective molecule against scoliosis progression. These molecules are measured in the blood of asymptomatic patients at different stages of the disease. Initial trials revealed that plasma OPN elevation is directly linked with AIS onset and severity of the disease; with severe cases (spinal curve in excess of 45°) demonstrating higher levels of OPN than patients with milder cases of scoliosis. Conversely, AIS patients with the mildest forms of the disease showed the highest levels of sCD44, as the molecule prevents OPN from triggering scoliosis, halting the progression of spinal deformity.

Moreau’s innovative prognostic techniques could vastly improve quality of life for scoliosis patients, delaying or even nullifying the need for invasive and often very painful treatments. Moreover, combining prognostic assays for scoliosis with new clinical techniques could facilitate the placing of patients at high risk of disease progression for placement at the top of surgical waiting lists, before their spinal deformity becomes too advanced. This has many advantages, including the fact that less deformed spines of younger patients are easier to correct due to increased flexibility; and earlier interventions more often lead to successful outcomes, with faster patient recovery.
recovery, reduced risk of complications and reduced health-related expenditure.

INTERNATIONAL VALIDATION

Moreau is presently supervising two major clinical collaborations for the validation of his two predictive scoliosis blood tests. As the Founder and Scientific Director of the International Consortium on Scoliosis (ICONS), he has chosen to conduct these international trials at the Istituto Ortopedico Galeazzi in Milan, Italy and the Prince of Wales Hospital in Hong Kong, China. Funded by Fourth Dimension Spine, these trials enable the research teams to validate the biochemical and genomic markers in specific populations (French-Canadian, Italian and Chinese), cross-referencing these data with established and comprehensive clinical, biochemical and functional information.

The opportunity to examine different populations across the globe is extremely valuable for replication studies, which will contribute to the development of universal comprehensive scoliosis diagnostic assays. Moreau thus brings together leading researchers and clinicians, working with interrelating goals to design and validate predictive tests for paediatric scoliosis, and other MSK diseases such as osteoarthritis (OA).

OSTEOARTHRITIS

Until recently, OA has represented an onerous challenge for researchers, due to the difficulty in diagnosing and characterising the disease: “X-rays and MRIs are commonly used, but there is ample scope for more effective alternatives to detect this disabling disease at the earliest stages,” Moreau reveals. His OA research has led to the discovery of unique molecular pathways, enabling the development of innovative OA blood tests.

Although less advanced than the scoliosis research, the group hopes that their work will lead to early interventions for undiagnosed symptomatic OA. These interventions would not only confirm the presence of the disease but would also enable doctors to choose the best treatment path for the patient. In parallel, early OA screening (before the disease has progressed to the stage of irreversible cartilage lesions) could enable pharmaceutical companies to adjust existing drugs that are not currently effective. Furthermore, detecting OA biomarkers in people who play high impact sports or engage in strenuous work activities would enable physicians to give advice on adapting their lifestyles to reduce the damaging factors that can lead to OA development. As there is no cure for OA at present, preventing the progression of the disease is vital to preserving patient quality of life.

THE FUTURE OF MSK RESEARCH

Alongside his contribution to the advancement of MSK research, Moreau has dedicated time to mentoring the next generation of pioneering Canadian researchers. He endeavours to develop the research capabilities of students from around the world with the aim of improving the quality of life for people incapacitated by MSK diseases. To achieve this he combines biomedical research with its application in clinical settings. For example, in 2006-13, Moreau’s tenure as Associate Director of Academic Affairs at CHU Sainte-Justine saw him contribute to the academic development of more than 425 graduate students from different university departments and programmes. Moreover, at CHU Sainte-Justine he participated in the development of the International Excellence Postdoctoral Scholarship and Award programme, which was so successful it led to a 234 per cent increase in the number of postdoctoral fellows at the university.

As Director of the Viscogliosi Laboratory in Molecular Genetics of Musculoskeletal Diseases, Moreau has built a multidisciplinary team of around 25 scientists, graduate students and researchers to address challenges in the field of MSK diseases. He also participates in the MENTOR training programme in MSK health, funded by CIHR, which is a platform for the development of numerous multidisciplinary research teams from different institutions in Montreal. Adopting a unique approach to teaching, trainees are supervised by two distinct mentors in order to widen their research scope within different research environments and laboratories. “An important goal of mine is to foster a high degree of team spirit, principled and personal commitment, and excellent human values so that these collaborative efforts result in the discovery of health solutions,” Moreau concludes.