

## **Areas of Excellence Scheme – Highlights of Achievements Developmental Genomics and Skeletal Research**

Degenerative disorders of the lumbar spine (DDD), lead to low back pain, thence to disability and suffering globally. Other disorders are caused by disturbances in skeletal development and growth. Understanding the biology of cartilage and bone is vital for progress in the treatment of degenerative skeletal disorders such as osteoarthritis and DDD. The University of Hong Kong (HKU) led AoE programme “*Developmental Genomics and Skeletal Research*” (2004-2014), was one of the few, worldwide, that took large-scale, multidisciplinary, multi-pronged approaches, combining molecular, biochemical, cellular, developmental and *in vivo* models with genomic, genetic and clinical studies, to address key issues in skeletal biology such as: *how normal skeletal growth is regulated. How skeletal integrity is maintained. How gene mutations cause skeletal disease. What genetic factors affect predisposition for degenerative skeletal disorders especially those leading to back pain?* Answers can, in the long term, be translated for strategies for skeletal tissue reconstitution and repair for better healthcare and quality of life for the millions of people suffering from musculoskeletal problems.

### **Establishing Research Excellence**

This programme involved concerted collaborative efforts of scientists and clinicians, from Hong Kong and internationally (Japan, Germany, Finland, UK, USA). The team delineated molecular controls for cartilage formation, maturation and skeletal growth, mechanisms of some congenital skeletal disorders and identified new factors for genetic susceptibility to degenerative intervertebral disc disease (DDD). Exciting discoveries were made, changing concepts of fundamental processes in skeletal biology and disease. The discovery that cartilage cells (chondrocytes) can become bone cells in normal skeletal development and bone repair, resolved a century long debate on the fate of chondrocytes and provides a conceptual shift, with important implications for bone biology and disease. A cellular molecular motor that controls chondrocyte organization and proliferation in the growing bone was discovered. A world class Transgenic Core Facility was established for *in vivo* studies and generation of disease models. Mouse models of human congenital skeletal diseases generated, yielded new insights into underlying molecular mechanisms. A type of human dwarfism was found to be caused by the impact of the impaired ability to assemble and secrete proteins. Genomic instability was implicated in a premature aging disorder. A new mechanism controlling digit outgrowth that determines the progression of joint formation, was discovered to underlie a skeletal disorder characterised by short fingers. A new genetic risk factor was found for low bone mineral density.

Through the AoE programme, the world’s largest population-based DDD cohort of over 3500 individuals with defined MRI and clinical phenotypes, was established. This cohort enabled the team to identify 3 novel genetic risk factors for DDD, to establish non-invasive methods to detect symptomatic intervertebral disc and pain generators. Juvenile disc degeneration and low back pain were associated with overweight and obesity. The exceptional performance of the programme has been highly praised by external experts, comprising leaders in the fields of skeletal research, genetics, functional genomics and systems biology.

## **Impact and Translational Potential**

The AoE programme have earned international recognition and placed Hong Kong research on the world-stage. Through this programme, the concepts of fundamental processes in skeletal biology and disease are changed. The clinical and genetics data also altered the mindset of clinician on the cause of low back pain, resulting in enhanced diagnostic ability and indications for treatment. This programme has important translational potential. US, European and Chinese Patents were issued for a mouse model of increased bone mass and high-affinity nucleic acid “aptamers” against drug targets to treat skeletal disease. Potential development of diagnostic markers and blockers to degenerative/pain pathways, prognostic genetic test kit and screening tests for DDD, and drugs modulating protein folding and intracellular clearance to treat some forms of osteochondrodysplasia and common degenerative diseases are now achievable.

## **Publications and Awards**

The discoveries were published in high quality journals such as *Nature*, *Nature Medicine*, *J. Clinical Investigation*, *Proceedings of the National Academy of Sciences (USA)*, *PLoS Biology*, *PLoS Genetics*, *American Journal of Human Genetics*, *EMBO J*, *Arthritis & Rheumatism* and *The Spine Journal*. A total of 168 papers and 400 conference abstracts were published. Many (69) prizes/awards were won, notably the Henry Farfan Award (North American Spine Society): 2008 - for outstanding contributions in spine related basic science research. Members have been honoured by invitations to speak at international conferences, by the election as Fellow of The World Academy of Science, election to leadership positions in international societies such as International Society for Matrix Biology, Societe Internationale de Chirurgie Orthopedique et de Traumatologie (SICOT), International Society for the Study of the Lumbar Spine (ISSLS).

## **Education and Training Opportunities for Local Scientists**

This AoE programme has trained 20 MPhil, 51 PhD students and 28 post-doctoral fellows (PDF) and contributed to the career progression of investigators. Three members recently received the prestigious Croucher Senior Fellowship awards.

## **Knowledge Exchange**

Members have contributed to public understanding of skeletal disorders through contribution to news media, TV programmes, and by leading organisation of Croucher Foundation Advanced Study Institutes and Symposia. They have played leadership and advisory roles in the establishment of the “*Little People of Hong Kong Foundation*” for public education and support for families with rare skeletal diseases. See <http://www.lphk.org/>.