Mini-Symposium

“Bone metabolism and diseases”

Centre Hospitalier Universitaire Vaudois (CHUV) Lausanne, March 12, 2014
Auditorium Yersin, CHUV main building, 8th floor
Organiser: Prof. Laurent Schild

PROGRAM

8:00 – 8:30 Welcome coffee

8:30-8:40 Welcome: Prof. Laurent Schild, UNIL, Lausanne, Switzerland

8:40 -9:25 Prof. Roland Baron (Harvard Medical School, Boston, MA)
"Cellular and molecular basis of skeletal homeostasis: translational implications in bone therapeutics"

9:25-10:10 Prof. Geert Carmeliet (Clinical and Experimental Endocrinology, University of Leuven, Belgium)
“Blood vessels in bone development and pathology”

10:10 – 10:30 Coffee Break

10.30-11.15 Prof. Roger Bouillon (Clinic and laboratory of experimental medicine and endocrinology, KU Leuven, Belgium)
“Vitamin D is a multifunctional hormone: intestine, bone and immune system as target tissues”

11.15-12.00 Prof. Serge L. Ferrari (University Hospital Geneva, Switzerland)
"Mechanisms of parathyroid hormone action on bone"

12.15 – 14.00 Lunch

14:00 – 16:00 Afternoon workshops for PhD students with symposium speakers

This mini-symposium will be accredited by the Swiss Association of Cantonal Veterinarians (SCAV) as a half day of continuing education.

This meeting is free of charge but for organization purposes we would like participants (limited to a maximum number of 120) to register by filling the form here prior to March 2, 2014.
The UNIL doctoral school attributes 1.0 ECTS for PhD students who present a signed participation form for the mini-symposium (0.25 ECTS morning session, 0.75 ECTS afternoon session).
For additional information, please contact Dr. Ulrike Toepel (ulrike.toepel@unil.ch).
**Talk abstracts**

**Prof. Roland Baron (Harvard Medical School and Sand School of Dental Medicine)**

"Cellular and molecular basis of skeletal homeostasis: translational implications in bone therapeutics"

In this lecture Dr Baron will briefly summarize our current understanding of the differentiation and function of bone cells and their cross-talk to regulate bone remodeling and ensure skeletal homeostasis in the adult skeleton. The Paracrine and endocrine regulation of these processes, occurring in bone, will be discussed as well as the newly recognized role of bone as an endocrine organ itself affecting the function of other organs such as the kidney, the brain, energy and glucose metabolism and hematopoiesis. The implications of these findings and of the genetic understanding of rare diseases on the development of novel therapeutic approaches for skeletal diseases will also be discussed.

**Prof. Geert Carmeliet (Clinical and Experimental Endocrinology, University of Leuven, Belgium)**

“Blood vessels in bone development and pathology”

Angiogenesis and osteogenesis are closely linked during bone development. Vascular endothelial growth factor (VEGF), a potent angiogenic factor, is critical for the timely formation of blood vessels during endochondral ossification has been evidently shown by the analysis of several transgenic mouse models. Moreover, a specific combination of soluble and matrix-embedded VEGF is required to correctly coordinate the different stages of endochondral ossification, like the formation of the primary and secondary ossification center. During this process, the expression of VEGF is regulated by transcription factors that also control the differentiation of osteogenic cells and hereby provides the synchronization of osteogenesis with angiogenesis. In addition, the rapid growth of the avascular growth plate causes the centrally localized chondrocytes to become hypoxic. Chondrocytes respond to this stress condition by switching on the hypoxia signaling pathway that attracts new blood vessels to deliver oxygen and nutrients for further growth and differentiation. In addition, the metabolic reprogramming of the chondrocytes is an important defense mechanism of these cells to survive. Also after bone fracture, cells have to adapt and respond to hypoxia and hereby initiate a repair process that closely mimics the different stages of bone development. Successful bone healing thus requires the timely reestablishment of a functional vascular network and the periosteum has an important role in this process. Finally, angiogenic factors in the bone environment may also contribute to the initial phases of bone metastases by creating a supporting niche for breast tumor cells to survive and proliferate. Recent findings on the role of blood vessels, angiogenic factors and hypoxia signaling in bone development and pathology will be discussed.
**Cardiovascular and Metabolism PhD Program**

**Dr. Roger Bouillon (Clinic and laboratory of experimental medicine and endocrinology, KULeuven, Belgium)**

“Vitamin D is a multifunctional hormone: intestine, bone and immune system as target tissues”

The vitamin D endocrine system (D-endo) is essential for calcium and bone homeostasis. Absence of a functional VDR or CYP27B1 creates a severe rachitic bone phenotype in humans and mice as in severe vitamin D deficiency. The intestine is the key direct target for VDR as to defend serum calcium and bone homeostasis. Its direct effect on bone are more complex as the vitamin D endocrine system will primarily defend systemic calcium homeostasis even at the (transient) expense of bone homeostasis. The implications for humans are multiple: rickets is still endemic in different parts of the world and milder forms of vitamin D deficiency is present in more than a billion people worldwide so that appropriate large scale strategies are needed to correct this situation.

VDR is ubiquitously expressed and about 3% of the mouse or human genome is regulated by D-endo. All cells of the immune system express VDR. A large number of immune-related genes are coherently controlled by 1,25(OH)_{2}D. The native immune system is stimulated by 1,25(OH)_{2}D whereas the acquired immune system is suppressed. The generation of T regulator cells is enhanced via direct and indirect effects. Therefore, the native immune defense system is activated by D-endo but VDR or vitamin D deficiency leads to increased sensitivity to autoimmune diseases such as inflammatory bowel disease or autoimmune diabetes after exposure to predisposing factors. A low vitamin D status is associated with an increased risk for all types of infections and especially pulmonary infections and tuberculosis. Intervention studies however are equivocal. The link between vitamin D and autoimmune diseases is suggested in human genetic studies, and in many animal models of autoimmune diseases like type 1 diabetes and multiple sclerosis. In man, epidemiological studies confirm such associations, but intervention studies till now fail to show preventive effects. Prospective and intervention studies are needed and ongoing as to define the optimal vitamin D status for global health.

**Prof. Serge L. Ferrari (University Hospital Geneva, Switzerland)**

"Mechanisms of parathyroid hormone action on bone"

By its direct actions on bone and kidney, parathyroid hormone (PTH) is the major regulator of serum calcium homeostasis. Yet PTH is also the only bone “anabolic” agent currently approved for treatment of osteoporosis. Hence PTH exerts paradoxical effects on the skeleton, i.e. stimulates bone resorption as well as bone formation, depending on its dose and duration of exposure, and on the bone compartment considered (cortical or trabecular). At the cellular level, PTH intracellular signaling and effects on gene expression are regulated by post-receptor mechanisms involving PTHrC phosphorylation and interaction with cytoplasmic proteins. Hence internalization and trafficking of the PTH-PTHrC complex with the intracellular adaptor protein beta-arrestin has been visualized by real time fluorescence microscopy and the receptor structural determinants of this interaction identified by site-directed mutagenesis. In turn, PTH administration to beta-arrestins-deficient mice has shown the influence of this signaling regulatory pathway on PTH bone resorbing/forming activities. Ultimately, PTH-stimulated bone resorption and formation as well as the coupling between these two activities is mediated by a variety of molecules expressed by osteoblasts and osteocytes, among which RANK Ligand and its antagonist, osteoprotegerin (OPG); IGF-1; PTHrP; sclerostin, and the matricellular protein periostin, among others.