



**UBC Dentistry Research Day 2019: Regenerate**

Tuesday, January 22, 2019 | Alma Mater Society Student Nest, Great Hall



**DR. HANNU LARJAVA** graduated from the University of Turku, Finland, in 1978 (DDS) and earned his PhD from the same institution in 1984. He then specialized in periodontics (1987) and moved to the NIH for a postdoctoral fellowship. After that he worked for 1.5 years as an Associate Professor at the University of Alabama in Birmingham engaged in research and clinical teaching. In 1993, Dr. Larjava was appointed as the Chair, Division of Periodontics at the University of British Columbia. Currently, he serves as Professor and Head of the Department of Oral Biological & Medical Sciences. Dr. Larjava has an active research interest in the pathogenesis of periodontal disease and oral wound healing and has published over 200 papers and book chapters. He has lectured nationally and internationally at numerous CE courses and conferences.

**OVERVIEW OF ORAL SOFT TISSUE WOUND HEALING**

Many everyday clinical procedures in modern dentistry relate to either soft or hard tissue wound healing. Soft tissue trauma and periodontal and oral surgery procedures cause wounds in the soft tissues of the oral cavity. Clinicians have observed relatively little scarring of oral mucosa, especially gingiva and palatal mucosa. We have confirmed in systematic human and animal models that palatal mucosa heals clinically with relatively little scarring compared to skin. In this presentation, the results from these clinical studies will be presented. In addition, histological and molecular data from these studies indicate that the tissue architecture, gene profiling, and molecular markers in the palatal mucosa are largely normalized in 2 months while scar markers continue to dominate in the skin. Factors causative to scarless healing in palatal mucosa remain incompletely known but faster resolution of inflammation and fibroblast phenotypes could be involved.



**DR. LARI HÄKKINEN** obtained his DDS and PhD degrees at the University of Turku, Finland. After postdoctoral research at the University of British Columbia, he joined the UBC Faculty of Dentistry in 1999, where he is currently a Professor in the Department of Oral Biological & Medical Sciences. He is also a member of the Cell & Developmental Biology Graduate School at UBC. Dr. Häkkinen has published more than 100 papers, mostly on wound healing and cell biology.

**CAN WE REGENERATE SKIN WOUNDS WITH ORAL CELLS?**

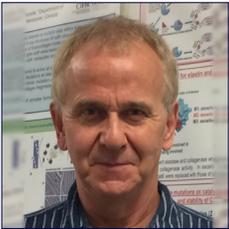
Wound healing in oral mucosal gingiva progresses faster and produces less scar tissue than skin wounds, which are prone to pathological scarring (hypertrophic and keloid scars), a significant clinical problem. The preferential gingival wound healing may depend on a distinct phenotype of gingival fibroblasts compared to skin fibroblasts. For instance, gingival fibroblasts have a different developmental origin compared to skin cells and display a distinct gene expression profile that may be conducive for fast and relatively scar-free wound healing. Therefore, tissue engineering approaches using gingival fibroblasts may provide novel ways to promote skin wound healing and prevent pathological scar formation. This presentation summarizes our recent findings about distinct properties of gingival fibroblasts and approaches to test their utility to promote wound healing in skin.



**PROFESSOR CHRISTOPHER OVERALL** is a Tier 1 Canada Research Chair in Protease Proteomics & Systems Biology and a Senior Fellow of the Freiburg Institute of Advanced Studies, Albert-Ludwigs Universität Freiburg, Germany, where he is now an Honorary Professor. He was inducted as a fellow of the Royal Society of Canada, Academy of Science in 2018. Dr. Overall is best known for his development of proteomic methodology for the discovery of protease substrates *in vivo*, thereby establishing the field of degradomics. He has used these techniques to reveal new biological roles for proteases in immunity and disease as well as new treatments to correct protease deficiency in an immunodeficiency disease. His > 270 papers have high impact with an h-index of 87.

#### **REGULATION OF INFLAMMATION AND WOUND HEALING**

In contrast to the traditional view of matrix metalloproteinases (MMPs) as matrix degraders, we show that MMPs are protective in inflammation. We explored the roles of the immune-modulatory MMP2 and macrophage MMP12 by quantifying global proteome, protein N-termini (the N-terminome), and the altered abundance of proteases and inhibitors in inflammation. Cleavage and inactivation of the C1 inhibitor by MMP2 increased complement activation and bradykinin generation, leading to increased vessel permeability during inflammation and hence influx of acute response proteins. *Mmp12*<sup>-/-</sup> mice were protected from viral endocarditis and display earlier and dramatic severe arthritis vs. wild-type mice characterized by massive neutrophil infiltrations. Overall, MMP12 is essential for INF $\alpha$  secretion and dampens inflammation by concerted cleavages in multiple inflammation regulatory pathways. Such examples exemplify the general renaissance MMPs are enjoying from matrix remodellers to key cell regulators of extracellular homeostasis. By developing degradomics strategies to explore the roles of proteases *in vivo*, many new substrates and hence functions in diverse processes have been revealed in regulating inflammation and immunity.



**DR. DIETER BRÖMME** received his PhD from the Martin Luther University of Halle-Wittenberg, Germany, in 1983 and developed a life-long interest in protease research. Before joining the University of British Columbia as a Professor and Canada Research Chair of Proteases & Diseases in 2004, he had academic and industrial positions at the NRC Biotechnology Research Institute in Montreal, Khepri Pharmaceuticals in South San Francisco, and the Mount Sinai School of Medicine in New York. Dr. Brömme has supervised more than 80 trainees, published nearly 200 papers including book chapters, and has several patents.

#### **SELECTIVE INHIBITION OF BONE EROSION: RESCUING OF A DRUG TARGET**

Cysteine cathepsins are powerful extracellular matrix-degrading proteases involved in musculoskeletal and cardiovascular pathologies. Among these enzymes, cathepsin K is the most-studied drug target for osteoporosis and active site-directed inhibitors proved highly efficacious in clinical trials. However, none of these inhibitors were FDA-approved due to various side effects. Our work suggests that this is due to on-target drug effects on a multifunctional protease, which can be overcome by substrate-specific *ectosteric inhibitors*. This talk will illustrate how ectosteric sites and their inhibitors were identified, how their *in vitro* and *in vivo* efficacy and specificity were characterized, and how the side effects of the cathepsin K inhibitors were overcome.



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