RTG 1830
GERMAN CANADIAN
COMPLEX MEMBRANE PROTEINS
IN CELLULAR DEVELOPMENT AND DISEASE

P12

The physiological and pathophysiological role of Sec63 protein in human cells (Sven Lang, Richard Zimmermann)

The protein translocase, which is present in the membrane of the mammalian endoplasmic reticulum (ER) is involved in the biogenesis of many soluble and membrane proteins at the ER. The translocase comprises the Sec61 complex plus its interaction partners Sec62 and Sec63. The Sec61 complex provides an aqueous path for the entry of nascent and completed polypeptides into the membrane or lumen of the ER. The Sec63 protein is supposed to recruit the ER lumenal chaperone BiP to the Sec61 complex and in this way to support BiP in playing one or more of its roles in protein transport into the ER, protein folding and/or assembly in the ER. The functions of mammalian Sec63 protein in transport and folding/assembly of proteins will be studied at the molecular level. On the one hand, the effect of siRNA-mediated knock-down will be analyzed in established murine and human model cells with respect to import of various model proteins into the ER and with respect to their folding within the ER. On the other hand, a proteomic approach will be employed in order to identify proteins that depend on Sec63 function in their biogenesis. This analysis will be extended to murine and human cholangiocytes because these are thought to be the cells that give rise to the formation of multiple cysts in polycystic liver disease (PLD). This human hereditary disease is linked to a loss of function of the *SEC63* gene and is supposed to be related to polycystic kidney disease (PKD) in its etiology. At present, loss of Sec63 function is speculated to lead to problems in either transport or folding/assembly of a subset of plasma membrane, organellar, or extracellular proteins that, under physiological conditions, control cell proliferation and/or planar cell polarity. Thus, our planned work also addresses questions that are related to the etiology of PLD. For comparison, we also have access to PLD patient material (through a collaboration with J. Drenth, NL, the European expert in PLD who discovered the link between PLD and the *PRKCSH* gene that also causes the disease).