Epigenetics

Bench to Bedside

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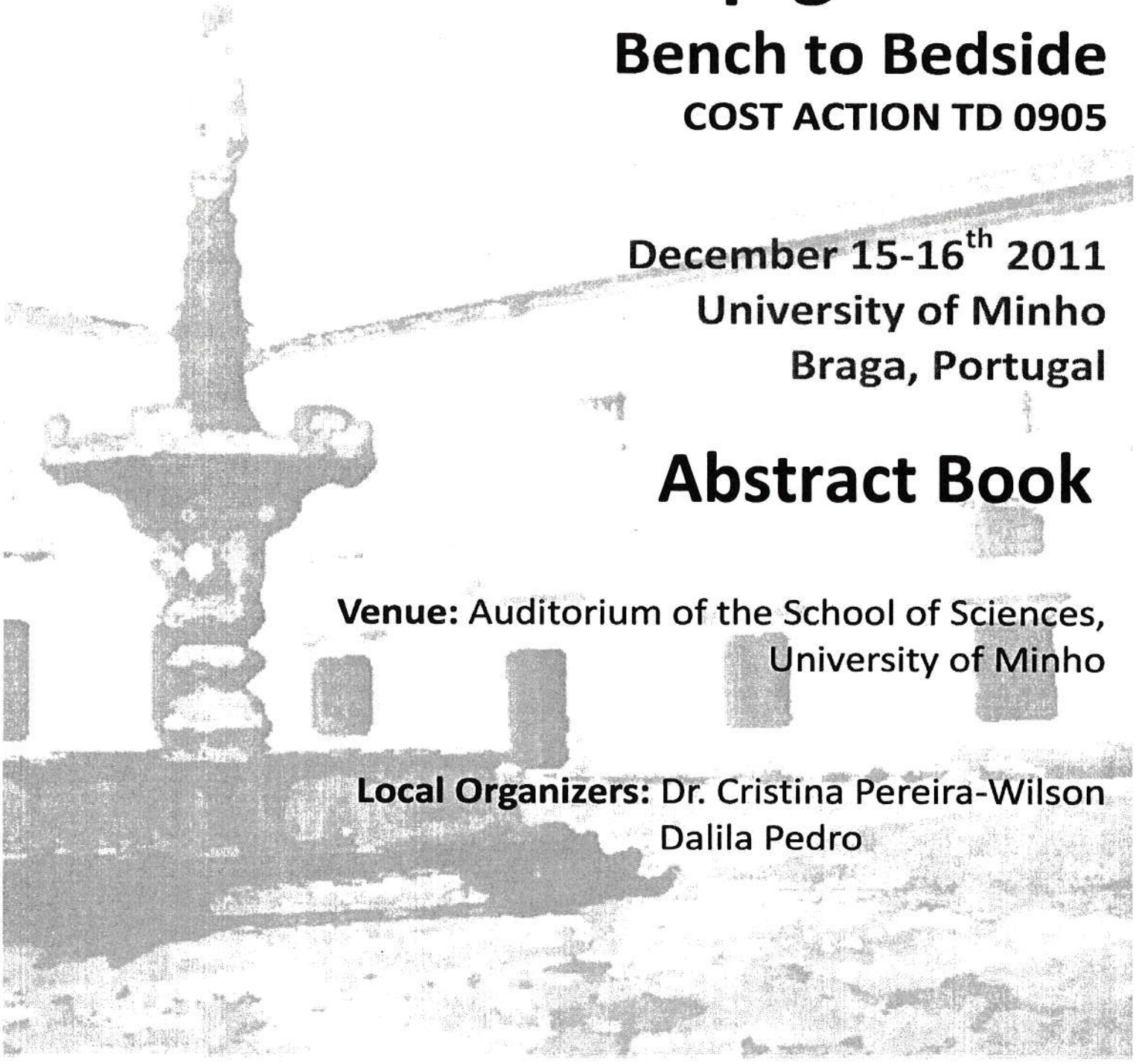

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Genetic prediction of type 1 diabetes and novel approaches for preventing pancreatic beta-cell dysfunction: examination of different stages of cxcl12-mediated signalling

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Contributing factor in the development of diabetes is a relative reduction in beta cell mass. Therefore, examiniation of factors that regulate beta cell growth and survival is important. CXC chemokine, CXCL12, enhances beta cell survival by the activation of the prosurvival kinase Akt and protects mice against streptozotocin-induced diabetes. The observation that CXCL12 is induced in tissues in response to injuries and that its receptor, CXCR4, is constitutively expressed on beta cells, led to the proposal of an autocrine feed back loop: injury of beta cells (glucotoxicity, cytokines) in diabetes induces CXCL12 expression and acts back on CXCR4 to further activate its own expression and to activate Akt-mediated signaling pathways that exert cytoprotective effects. On the other hand, inhibition of polyADP-ribose polymerase 1 (PARP-1) enzyme promotes pancreatic beta cells survival and prevents experimentally induced diabetes. Besides, PARP-1 inhibition is in correlation with Akt activation. Based on these data we wanted to assess what is the connection and interplay among CXCL12, Akt and PARP-1 in beta cell survival. Our results suggest that PARP-1 and CXCL12 activities are involved in the regulation of beta cell survival and that CXCL12 signaling pathway affects PARP-1 activity. For the first time we connected CXCL12, Akt and PARP-1 molecules proposing that CXCL12 signaling cascade activates Akt which in turn phosphorylates and inhibits PARP-1. We are planing to involve epigenetic approach to our researh because understanding of the molecular changes of chromatin structure and their functional relationship with altered signaling pathways is now considered to represent an important conceptual challenge to explain diabetes. Because PARP-1 inhibits DNMT1 and is a positive regulator of epigenetic stability by protecting CpG islands from aberrant hypermethylation, we will include PARP-1 in our future epigenetic research with the aim to explore weather PARP-1 is part of the epigenetic regulation in diabetes. We will assess and compare DNA methylation pattern of control and diabetic pancreatic β cells before and after treatment with PARP-1 inhibitor(s). We are intending to test in vitro DNMT1 inhibitors

on rat pancreatic insulinoma cell line (Rin-5F), cultured rat pancreatic islets isolated from control and diabetic animals and human pancreatic islets obtained from patients underwent surgical removal of the pancreas (including diabetic patients). We would like to examine if mechanism of action of the DNMT1 inhibitors includes PARP-1 enzyme involvement.