A nanomedicine approach for diabetes: targeting the NLRP3 inflammasome in tissue-resident macrophages.

Heather Denroche¹,⁴, Nahae Kim¹,⁴, Alex Hsu¹,⁴, Sam Chen⁴, Joshua Zaifman²,⁴, Ying Tam⁴, Chris Tam⁴, Marco Ciufolini²,⁴, Pieter R. Cullis³,⁴, C. Bruce Verchere*¹,⁴

¹Department of Surgery, University of British Columbia, Canada, bverchere@bcchr.ca; ²Department of Chemistry, University of British Columbia, Canada; ³Department of Biochemistry, University of British Columbia, Canada; ⁴Integrated Nanotherapeutics, Vancouver, Canada.

Type 2 diabetes (T2D) is a devastating disease with an enormous economic burden, caused by progressive loss of functional insulin-producing beta cells in the pancreas together with insulin resistance. Inflammation is a driver of T2D pathogenesis, in which macrophages in adipose tissue and pancreatic islets produce IL-1β by a mechanism involving activation of the NLRP3 inflammasome. Clinical use of anti-inflammatory drugs in T2D is hampered by lack of cell specificity and off-target side-effects, including liver toxicity. We are developing a nanomedicine therapeutic for T2D that will target the NLRP3 inflammasome specifically in macrophages, inhibiting local production of IL-1β and thus enhancing insulin sensitivity and beta-cell function. We have developed several effective pro-drug inhibitors of the NLRP3 inflammasome encapsulated in a lipid nanoparticle (LNP) formulation that preferentially targets macrophages. Ex vivo, our lead pro-drug inhibits IL-1β secretion by bone-marrow derived macrophages stimulated by canonical NLRP3 inflammasome activators. In vivo, our LNP formulation is selective for tissue-resident macrophages (including macrophages in pancreatic islets and in adipose tissue) compared to other cell types, and efficient (>95% of islet macrophages targeted). Administration of our LNP formulation reduced Il1b expression in pancreatic islets of non-diabetic mice, indicating effective drug delivery to islet macrophages. Furthermore, long-term administration (15 weeks) in mice did not alter circulating liver enzymes or show other signs of liver toxicity compared to controls. In future studies, we aim to test whether this LNP formulation prevents diabetes in mouse models of T2D.