Jason Hung

Type 1 diabetes (T1D) is a currently incurable autoimmune disease that affects roughly 35 million individuals worldwide and is caused by impaired glucose homeostasis due to the destruction of insulin-secreting β cells through a breakdown in immunological tolerance to β cell antigens. Several components involved in regulating and suppressing T cell activation by self-antigens are believed to be involved, including regulatory T cells (Tregs), dendritic cells (DC) and natural killer T (NKT) cells. To determine whether regulatory function of these cells can be restored in a model of T1D, we have assessed the preventive potential of a novel liposome that incorporates both the NKT agonist alpha-galactosylceramide (αGalCer) and insulin, a key early antigen involved in the disease pathogenesis. We hypothesized that stepwise activation of the DC, Treg and NKT pathways using this novel agent would prevent diabetes in NOD mice. Liposomal therapy or control agents were administered to NOD mice through different routes from week 4 to week 9 and mice were followed for hyperglycemia. We show that liposomal therapy prevents T1D in non-obese diabetic (NOD) mice compared to untreated mice and that the route of injection was paramount for efficacy. Intravenous injections provided no protection, intraperitoneal injections only delayed T1D, while subcutaneous injections fully protected mice from disease. Interestingly, there was no difference in insulitis scores between treatment groups despite disease outcome. We also show that αGalCer presentation occurs in macrophages and dendritic cells present in the epidydimal fat at 24 hours and 72 hours. We conclude that subcutaneous liposomal therapy using αGalCer and insulin can prevent the development of T1D in NOD mice. We propose that the liposome composition as well as the route of injection alters the

pharmokinetics and pharmodynamics of the therapy, possibly by increasing drug stability or by creating drug reservoirs in key organs.