The prevalence of diabetes has become an increasing concern to the world’s population. The potential of sodium-dependent glucose cotransporters (SGLTs) as a new family of drug targets for the treatment of diabetes has been realized over the past few decades. The SGLT family consists of several isoforms that actively transport sugars across cellular membranes, a process that is coupled with sodium ion transport. SGLT1 is primarily expressed in the GI tract where it is largely responsible for intestinal absorption of glucose and galactose. SGLT2 is primarily expressed in the proximal convoluted tubule of the kidney and reabsorbs 90% of plasma glucose filtered in the kidney. Currently approved SGLT inhibitors work on selective SGLT2 since inhibition of SGLT1 is undesirable due to GI side effects like life-threatening diarrhea. SGLT2 inhibitors, however, fail in patients with renal impairment that affects 50% of the diabetic population. Sotagliflozin, a dual SGLT inhibitor, currently in late-stage clinical trials exhibits no side effects from SGLT1 inhibition. The added benefit of SGLT1 inhibition has opened a new therapeutic window that is independent of kidney function.

Further structural modifications of Sotagliflozin led to discovery of LX2761, a chemically stable and potent SGLT1 inhibitor with a xyloside core that delays intestinal glucose absorption without side effects with IC$_{50}$ of 2.2 nM. The advantage is that it displays specific pharmacology attributed to SGLT1 inhibition that restricts the compound in the GI tract.

This seminar talks about the development of dual SGLT inhibitors and further emphasizes selective SGLT1 inhibition, specifically the structure activity relationship that lead to the discovery of LX2761 from Sotagliflozin. In addition, data from pharmacokinetic studies will be reviewed that show the compound inhibiting SGLT1 locally in the GI tract with minimal systemic absorption.

References: