Abstract
Cadmium (Cd²⁺) is a toxic metal found in the environment, a product of industrial pollution, and can enter the body through inhalation. Chronic exposure to Cd²⁺ causes kidney failure characterized by a Fanconi-like Syndrome, in which an array of sodium-dependent nutrient transport is inhibited. Cd²⁺ causes a concentration-dependent reduction in sodium-glucose co-transport that is correlated to the sodium-glucose transporter (SGLT1) gene expression in kidney proximal tubule epithelial cells. SGLT1 is regulated by a zinc finger transcription factor, Sp1. In the presence of Cd²⁺, the zinc ion is displaced by a Cd²⁺ ion, resulting in the loss of transcriptional regulation of SGLT1. The structure of human SGLT1 is not known. As such, the Shorewood SMART Team (Students Modeling A Research Topic) modeled a bacterial homolog of SGLT1 using 3D printing technology. The SGLT1 protein transmembrane helices (TM2E, TM3, TM7E, TM8, and TM11) and amino acids on these helices vital for Na⁺ dependent glucose co-transport are conserved. SGLT1 undergoes a conformational change enabling Na⁺ dependent glucose transport across the apical membrane of proximal tubule of kidney. In order to understand the glucose transport in the face of Cd²⁺ and to understand the underlying molecular mechanism responsible for SGLT1 glucose transport, it is essential to know the protein structure of SGLT1.

Introduction
Glucose, a nutrient acquired from food, is a vital energy source for the human body. During the filtration of toxins from blood in the kidney, glucose and other nutrients are also forced out of the bloodstream. Because glucose is an important energy source for the body, it needs to be reabsorbed into the bloodstream. It is the job of membrane transporter proteins, such as the sodium-glucose transporter (SGLT1), to transport glucose and other nutrients across the membranes of the nephrons - functional units of the kidney - and back into the bloodstream. Without properly functioning membrane transporter proteins like SGLT1, the reabsorption of glucose is decreased, and can lead to glucose deficient disorders such as glucosuria.

The Kidney
- The kidney is the human organ responsible for the filtration of blood.
- The functional unit of the kidney is the nephron.
- Steps of filtration:
  - Blood is pushed into the glomerulus under high pressure.
  - High pressure forces nutrients and toxins into the Bowman’s capsule.
  - Glucose and other nutrients are reabsorbed in the proximal tubule.
- SGLT1 is the protein responsible for the reabsorption of glucose over the apical side of the nephron’s proximal tubule.
- Each day, 180 g of glucose is filtered by the kidneys and almost all of it is reabsorbed by SGLT1.

SGLT1’s Function
- SGLT1 requires the presence of two sodium ions for every one molecule of glucose to be transported.
- With the introduction of sodium and glucose, SGLT1 structurally changes shape to channel sodium and glucose across the proximal tubule’s membrane.
- SGLT1 returns to its resting state after glucose and sodium have been reabsorbed, and the cycle repeats.

Cadmium and SGLT1
- Cd²⁺ is a metal found in the air, soil, and water as a result of industrial pollution.
- Cd²⁺ enters the body through inhalation.
- Kidneys take 1/3 of the load of total Cd²⁺ intake.
- Cd²⁺ has a very long half-life in the kidney cortex.
- Cd²⁺ inhibits SGLT1 and causes glucosuria by:
  - Deformation of Sp1 (an important transcription factor for SGLT1 that has a zinc finger motif)
  - Cd²⁺ displaces zinc and structurally deforms Sp1.
  - Deformed Cd-Sp1 is incapable of transcribing the SGLT1 gene.
  - Results in the reduction of SGLT1’s mRNA and protein.

Summary
SGLT1 is an important protein to study, as it is responsible for the reabsorption of glucose, a primary energy source. Cd²⁺ plays an inhibiting role on this protein and can cause glucosuria. Since glucose can have such an effect upon the human body, it is important to be aware of the effects of Cd²⁺ upon SGLT1 and other proteins. Additionally, many people live near sites of Cd²⁺ pollution, and are exposed to it daily.

References