Nanoparticles (NPs) are poised to have a tremendous impact on the treatment of many diseases, but their broad application is limited because currently they can only be administered by parenteral methods. Oral administration of NPs is highly preferred because of the convenience and compliance by patients, but remains a significant challenge because of the barriers presented by the gastrointestinal tract. In particular, transport across the intestinal epithelium limits efficient oral delivery of NPs.

The neonatal Fc receptor (FcRn) mediates IgG antibody transport across epithelial barriers. It was discovered as the receptor in the neonatal intestine that transports IgG in breast milk from mother to offspring. However, FcRn is expressed into adulthood at levels similar to fetal expression. FcRn interacts with the Fc portion of IgG in a pH-dependent manner, binding with high affinity at acidic (<6.5) but not neutral pH (7.4).

Targeting NPs to FcRn using IgG Fc fragments was hypothesized to enable orally administered NPs to be transported across the intestinal epithelium. FcRn-targeted NPs were formulated using poly(lactic acid)-b-polyethylene glycol (PLA-PEG) block copolymers and engineered to have particle sizes less than 100 nm with IgG Fc conjugated to the surface. Transepithelial transport of the NPs was first evaluated in an in vitro cell monolayer transport model using Caco-2 cells. FcRn-targeted NPs were transported across the monolayer at a rate twice that of non-targeted NPs. The transport rate was reduced significantly when excess IgG was added along with the FcRn-targeted NPs.

Next, FcRn-targeted NPs were evaluated using in vivo mouse models. Fluorescent FcRn-targeted NPs were observed with fluorescence microscopy crossing the intestinal epithelium and entering the lamina propria after oral administration. Using radiolabeled NPs, orally administered FcRn-targeted NPs were detected in the liver, lungs, and spleen with a mean absorption efficiency of 13.7% for FcRn-targeted NPs compared with only 1.2% for non-targeted NPs.

Finally, insulin was encapsulated in the NPs to evaluate the FcRn-targeted NPs as a NP-based therapeutic. In wild-type mice, orally administered FcRn-targeted NPs containing insulin were able to generate a prolonged hypoglycemic response using a clinically relevant insulin dose of 1.1 U/kg. The response was specifically due to FcRn, as studies in FcRn knockout mice mitigated the enhanced response of the FcRn-targeted NPs.

This technology has the potential to have an impact on the treatment of many diseases by enabling NP-based therapies to be administered orally. In addition, the encapsulation of drugs or biologics that are currently limited by low bioavailability into FcRn-targeted NPs may enable markedly more efficient oral delivery of the therapies.