Developing an Oral Delivery Platform for siRNA Using Intelligent Nanotechnology Systems for Treatment of Inflammatory Bowel Diseases

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Current treatments for inflammatory bowel diseases (IBDs), include immunosuppressant drugs and parenterally delivered antibodies that target pro-inflammatory cytokines. These treatment methods require delivery systemically, reduce immune system performance, and are only effective in ~30% of patients. Further, parenteral delivery is not accessible for patients in poor areas of the world. The work discussed here develops an oral delivery platform for small interfering RNA (siRNA) for treatment of IBDs, which will improve accessibility of the therapy to the global population. siRNA can silence the production of specific strands of mRNA and is promising for the treatment for IBDs by silencing pro-inflammatory cytokines released by macrophages associated with disease propagation. Challenges associated with the oral delivery of siRNA include the harsh pH of the stomach, enzymatic degradation, uptake of siRNA into macrophages in the intestines, and the need to undergo endosomal escape following intracellular delivery. To achieve this, a multi-layered system is proposed and will be developed with an anionic coating that protects its payload through the stomach and expands to release siRNA-loaded cationic nanogels under neutral pH conditions in the intestines. Cationic nanogels based on 2-(diethylamino) ethyl methacrylate were synthesized exhibiting a pK_a~6 that promotes endosomal escape following uptake by macrophages. siRNA loading and release kinetics were evaluated, and the nanogels were non-toxic and successfully reduced cytokine expression by macrophages. Future work will focus on self-assembly of anionic methacrylic acid around the siRNA-loaded cationic nanogels. This dual layered platform can be applied to other autoimmune diseases in the future.

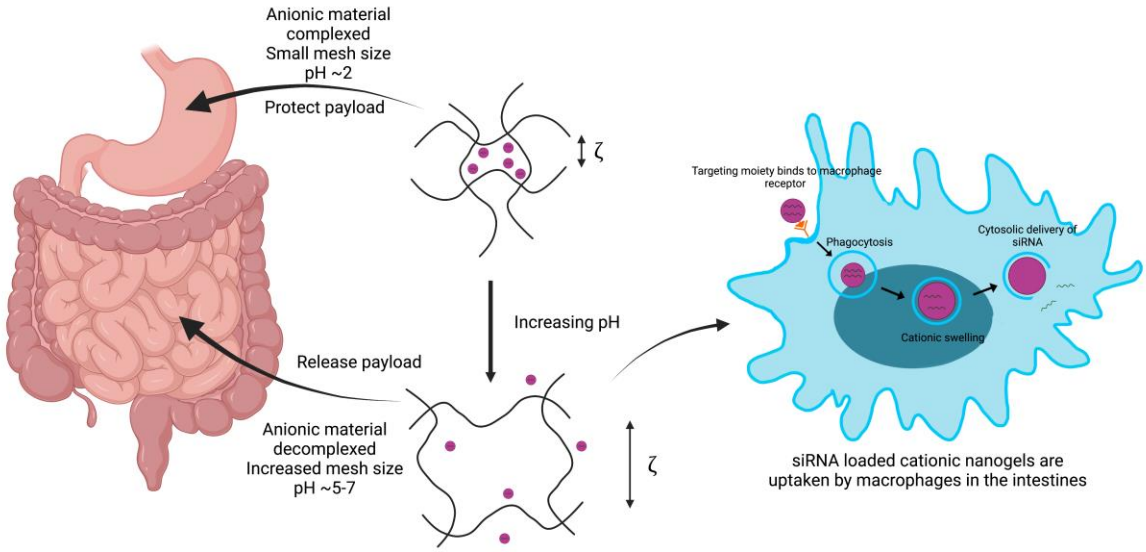

Figure 1. Anionic coating is complexed and protects siRNA loaded cationic particles through the acidic stomach. When arriving at the neutral pH environment of the intestines, the anionic material decomplexes and releases the siRNA loaded cationic particles. The cationic particles are targeted for uptake by disease associated macrophages. Inside the slightly acidic endosome, the cationic particles swell to initiate endosomal escape. siRNA is then released into the cytosol where it can silence mRNA transcription for inflammatory cytokines.