Synthesis and Knockdown Efficiency of Bone-Targeting Antisense Oligonucleotide Bioconjugate

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Antisense oligonucleotides (ASOs) have transpired as novel therapeutic agents to treat various diseases, revolutionizing drug discovery. ASOs are composed of short strands of single-stranded deoxyribonucleotide analogues that can specifically bind to target RNA and precisely modulate the expression of disease-causing proteins.[1] However, to date, ASOs have not been explored as potential treatment for bone disease. This is mainly due to their tendency to accumulate in the liver, kidneys and off target sites.[1] In addition, the unique histological features of the bone (*i.e.,* blood–bone marrow barrier) limits blood flow and therapeutic entry into skeletal sites, adding another level of complexity to bone targeting. Numerous studies have demonstrated the osteotropicity of bisphosphonates (BPs) and oligopeptides, providing bone targeting benefits for a range of biopharmaceuticals.[2] However, such bone targeting strategies have not been applied to deliver therapeutic ASOs to the bone, to date. On this basis, the primary aim of this research is to construct bone-targeting ASO bioconjugates and to investigate the role of various bone targeting moieties on *in vitro* knockdown efficiency and bone affinity.

A series of bone-targeting ASO bioconjugates were synthesized using different targeting moieties and linkers. A model ASO targeting *MALAT1* was conjugated to either an oligopeptide or bisphosphonate via a degradable (disulfide) or nondegradable linker (thioether). Subsequent characterization and *in vitro* knockdown efficiency studies to evaluate and compare the bioconjugates activity will be completed and reported. We hypothesize that bone targeting ASO bioconjugate will increase the *in vitro* binding affinity and knockdown efficiency of ASOs.

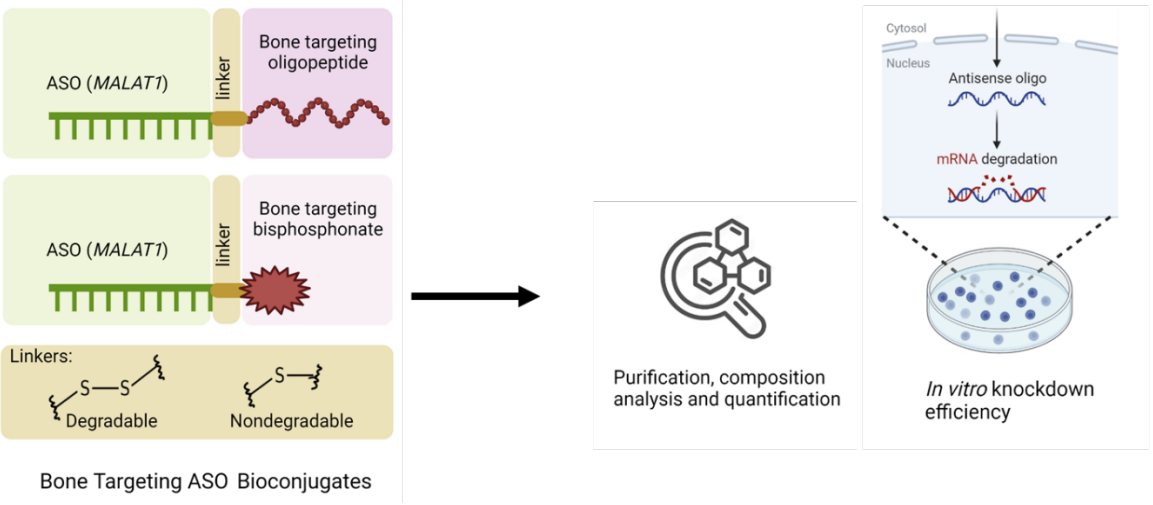

Figure 1: Composition and *in vitro* investigations of synthesized bone targeting ASO bioconjugates.

References

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(2) Rotman, S. G. *Journal of Controlled Release* **2018**, *269*, 88–99.