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Histological Response to Myostatin and Activin-A Antibodies in the G610C Osteogenesis Imperfecta Murine Model

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Osteogenesis imperfecta (OI), also known as brittle bone disease, is an incurable connective tissue disorder primarily caused by mutations in the type I collagen genes and phenotypically manifested in type I collagen-containing tissues, particularly bone. Our laboratory uses the G610C murine model to study OI, where wild type (WT) G610C mice do not exhibit increased susceptibility to fractures, skeletal deformities, and muscle weakness as seen in the heterozygous G610C mouse (+/G610C).

Bone is mechanosensitive and responds to high mechanical loads by stimulating new bone formation and altering bone geometry to withstand increased forces. Myostatin (mstn), a member of the TGF-β superfamily, is a negative regulator of muscle growth. Previous pharmacological inhibition of myostatin in +/G610C mice using the soluble activin receptor type IIB-mFc (sActRIIB-mFc) fusion protein resulted in increased hindlimb skeletal muscle weight with improved contractile function. The underlying molecular mechanism of sActRIIB-mFc remains unknown, and negative side effects in humans have been noted, likely due to the receptor's ability to bind multiple targets in addition to myostatin.

Among sActRIIB-mFc targets, myostatin and activin-A (act-A) are known to regulate bone and muscle growth. Thus, we treated male WT mice with isotype control-antibody, anti-myostatin (anti-M), or anti-activin-A (anti-A) specific antibodies for 11 weeks, starting at 5 weeks of age to investigate the impact of decreased circulating mstn and actA in bone growth and stability.

Bone is composed of three major cell types: osteoblasts, osteocytes, and osteoclasts. Osteoblasts are cells which secrete the matrix for bone formation. I have been performing histological examination of osteoclast numbers and sizes to determine the effects of myostatin antibodies (mstn-ab) and activin antibodies (act-ab) on cell numbers.

We hypothesize that postnatal inhibition of myostatin or activin-A would reduce osteoclast number and activity in G610C mice, though more data is needed to determine full effects on bone.