Fracture Targeted Parathyroid Hormone Agonist as an Effective Pharmaceutical for Bone Repair in Mouse and Canine Models

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Background

The goal of this project is to complete the lab-to-clinic translation of a drug that efficiently targets and promotes the rapid healing of fractured bones. Orthopedic injuries comprise a significant portion of training and combat-related soldier disability and medical expenditures. Indeed, ~65% of all wounds associated with military conflicts since WWI have included orthopedic injuries,[1] and 26% of all injuries to an extremity have involved one or more broken bones.

Fractured bones also constitute a prominent repercussion of military training exercises. While such maladies may at first seem trivial, statistics reveal that they cost the military ~$34,000[3] per soldier which totals up to ~$100 million in aggregate per year due to rehabilitation and recruits dropping out.[4]

Drug Design

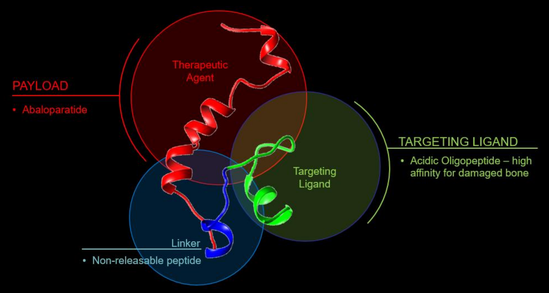


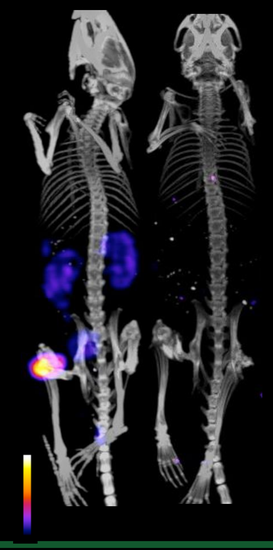
Figure 1: We synthesized a fracture targeted anabolic agent consisting of a bone anabolic (red) in tandem with a linker (blue) and a hydroxyapatite binding acidic oligopeptide (green).

Aims

We are developing a promising solution to this problem; namely, a potent and nontoxic fracture-targeted bone anabolic agent that is injected systemically but accumulates selectively on a bone fracture surface. The targeted therapy avoids the requirement for invasive surgery and eliminates the danger of ectopic bone growth while improving the rate and quality of bone fracture repair.

Bone-Targeting

Figure 2: GSK3β inhibitor labeled with ^{125}I and imaged at 24h using SPECT/CT. A) When the GSK3β inhibitor is conjugated to an acidic oligopeptide, the majority of signal is observed in the fracture callus of the femur, with trace concentrations of drug can observed in the kidneys and bladder, most likely en route to excretion. B) Free GSK3β inhibitor is quickly excreted and shows no affinity toward fractured bone



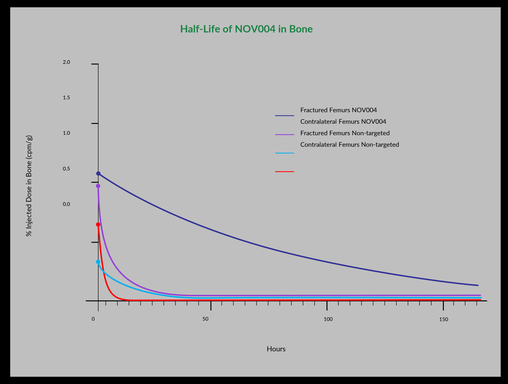


Figure 3: The half-life of NOV004 in the fractured bone is 10x that of non-damaged bone

Safety

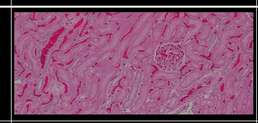
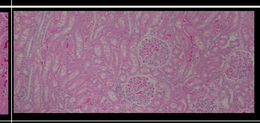
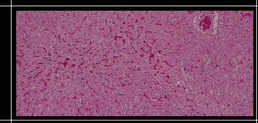
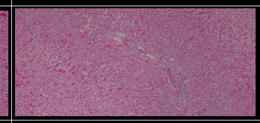
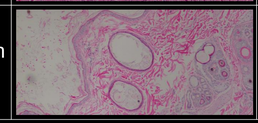
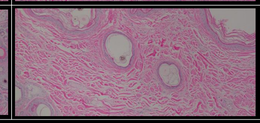
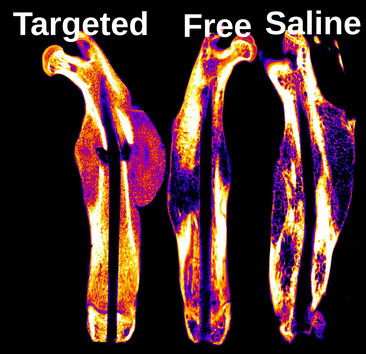
Tissue	Saline	10X dose of targeted abaloparatide
Kidney		
Liver		
Injection site		

Figure 7: Histology of treated and control Beagles after 19 weeks of daily s.c. dosing. No lesions were detected in a blinded study by a pathologist.

Fracture Healing



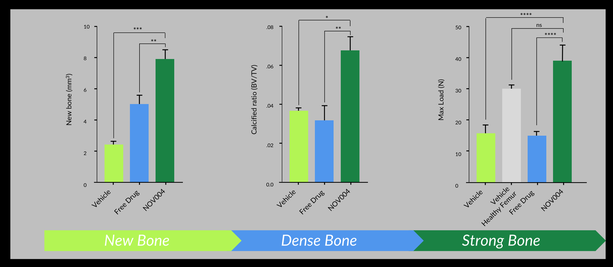
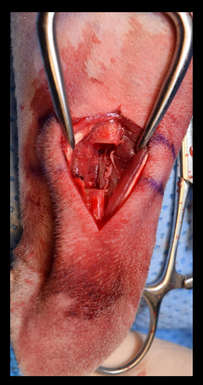


Figure 4 (left): Median micro-CT images from fractured mouse femurs in Figure 4. Each image is a composite of 50 microCT slices. Yellow and orange colors indicate higher bone densities than purple and blue. In general, the white/light yellow areas constitute original cortical bone and the cooler colors correspond to new trabecular and woven bone. NOV004 outperforms both the saline control and the free anabolic.
Figure 5 (right): Mechanical analysis of fractured mouse femurs 3-weeks post fracture after daily subcutaneous administration of NOV004



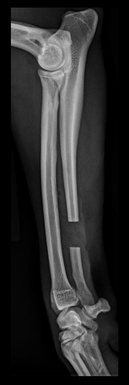
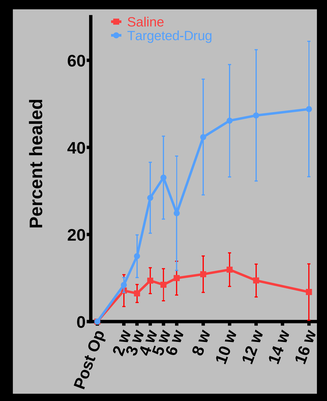


Figure 6: Canine *in vivo* experiments were conducted on 1-year-old male beagles. Beagles underwent a 10 mm bilateral ulnar ostectomy with 2 dogs in each treatment group and three dogs in the control group were dosed daily with either 1x NOV004 (0.5 nmol/kg/d), 10x NOV004 (5 nmol/kg/d, used for toxicity purposes) or saline control. After 4 weeks of treatment, the 1x treatment group exhibited a 3.5-fold smaller gap measured by x-ray than that of saline ($p<0.05$) . By the end of the experiment the targeted drug was 7.2-fold improved compared with saline control ($p<0.05$).



Discussion

To achieve our aims, we conjugated a bone mineral-(hydroxyapatite-) targeting oligopeptide to the non-signaling end of a bone anabolic agent. This negatively charged oligopeptide has been shown to target raw hydroxyapatite with incredible specificity, while therapeutic agent is known for its autocrine/paracrine signaling and stimulation of bone growth. Because raw hydroxyapatite is only exposed whenever a bone is fractured and extreme remodeling is occurring, the above conjugate drug can be administered systemically (i.e. without invasive surgery or trauma) and still accumulate specifically on the exposed hydroxyapatite of the fracture site where it accelerates fracture healing. We hope that a future combatant's fracture would be immediately stabilized by standard methods and then treated with a targeted potent bone growth stimulating drug, dramatically shortening their time on the disabled list and improving overall outcomes.

References

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