Re-engineering Abaloparatide To Target Fracture Repair Following Systemic Injection

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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. The annual frequency of bone fractures in the U.S. is approximately 6.3 Million.[1] Costs associated with conventional treatments and subsequent lost productivity carry a major economic burden--a problem compounded by an aging population. This increasing age demographic will continue to raise the frequency of osteoporosis and the associated rate of complicated and life-threatening fractures, with hip fractures expected to increase 160% to 500,000/year by 2040.[2] The total estimated expenses due to hip fractures in the elderly are $20 billion/year in the U.S. alone,[3] with half of patients unable to regain full mobility and a quarter dying within a year from associated complications.[4]

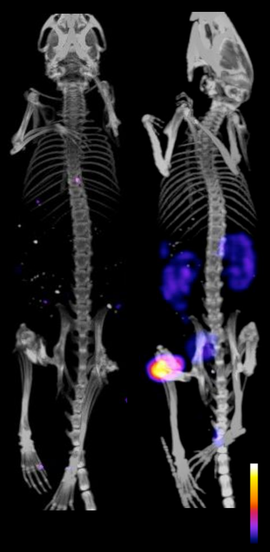


Figure 1: GSK3β inhibitor labeled with ^{125}I and imaged at 24h using SPECT/CT. A) When the GSK3β inhibitor is conjugated to an acidic oligopeptide, the majority of signal is observed in the fracture callus of the femur, with trace concentrations of drug can observed in the kidneys and bladder, most likely en route to excretion. B) Free GSK3β inhibitor is quickly excreted and shows no affinity toward fractured bone

Aims

We are developing a promising solution to this problem; namely, a potent but 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.

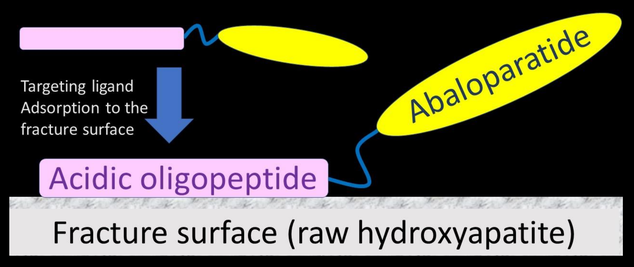
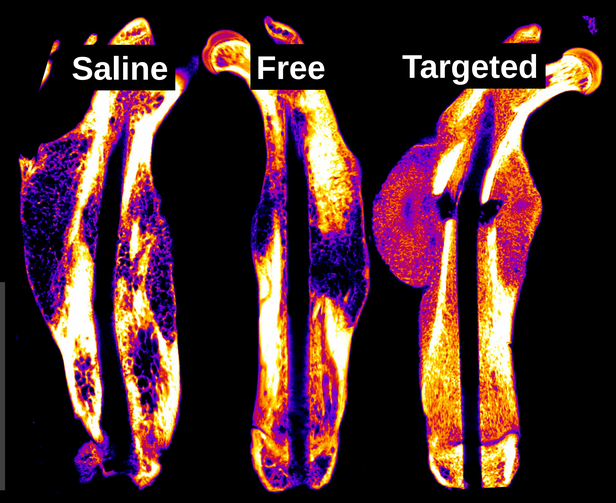


Figure 2: We synthesized a fracture targeted anabolic agent by synthesizing abaloparatide (yellow) in tandem with a spacer (blue) and a hydroxyapatite binding acid oligopeptide (magenta). This combination was selected for several reasons:

- Abaloparatide demonstrated similar effects as Forteo in osteoporosis clinical trials
- Works in a paracrine/autocrine manner, whereas Forteo functions in an endocrine process
- Simple administration (Subcutaneous dosing)



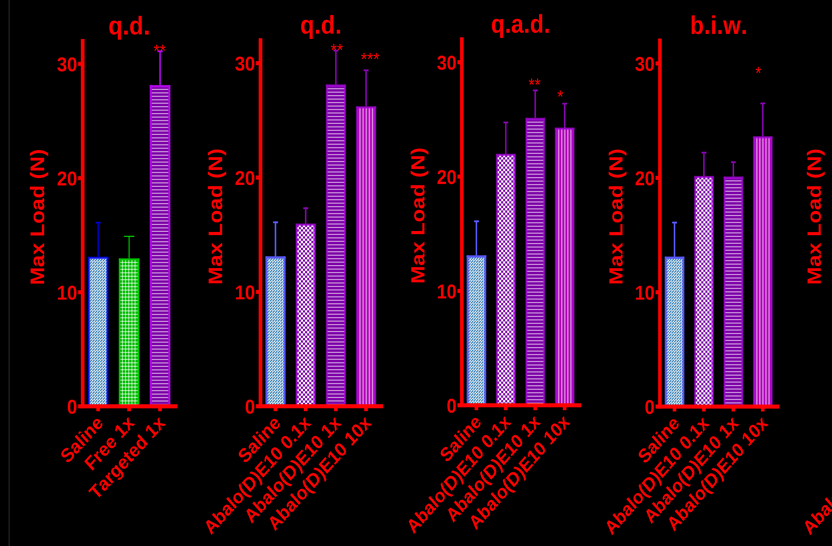


Figure 3 (above): Median microCT images from fractured mouse femurs in Figure 4. Each image is a composite of 50 microCT slices. The top of the image is the distal femur and the bottom is the proximal femur. Yellow and orange colors indicate higher bone densities than purple and blue. In general, the white/light yellow areas constitute original cortical bone and the cooler colors correspond to new trabecular and woven bone. The targeted abaloparatide outperforms both the saline control and free form of abaloparatide

Figure 4 (left): Mechanical analysis of fractured bones 3-weeks post fracture. Mice were dosed daily subcutaneously.

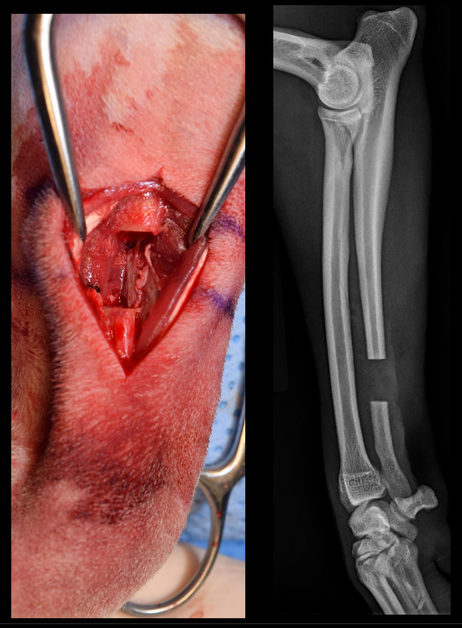
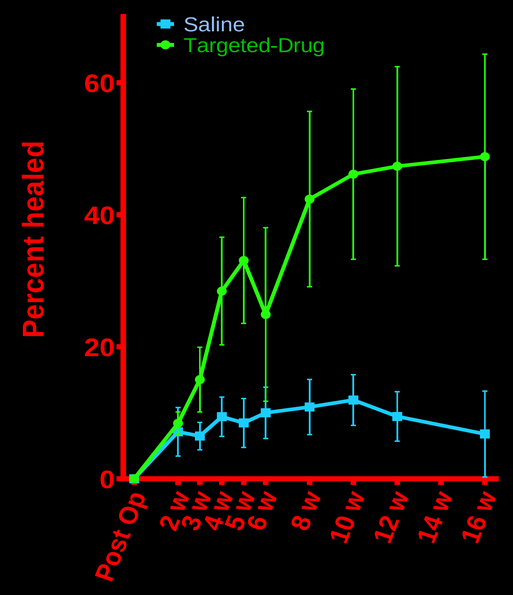


Figure 5: Canine *in vivo* experiments were conducted on 1-year-old male beagles. Beagles underwent a 10 mm bilateral ulnar ostectomy. Two dogs in each treatment group and three dogs in the control group were dosed daily with either targeted-abaloparatide 0.5 nmol/kg/d, 5 nmol/kg/d (10x group was used for toxicity purposes) or saline control. Dogs were x-rayed weekly for the first 6 weeks and then every other week thereafter. After 4 weeks of treatment, 0.5 nmol/kg/d of targeted-abaloparatide was 3.5 fold that of saline ($p<0.05$). By the end of the experiment the targeted drug was 7.2 fold that of the saline control ($p<0.05$).



	Kidney	Liver	Injection Site
Saline			
10x Abalo(D)E20 q.d.			

Figure 6: Neither gross nor individual tissue histology showed signs of toxicity even at 10x daily dose. All other standard blood chemistry panel levels showed no change from baselines. In addition, weights and heart rates were not significantly different between control and test animals, indicating a very safe targeted drug

Discussion

To achieve the our aims, we conjugated a bone mineral-(hydroxyapatite-) targeting oligopeptide to the non-signaling end (c-terminus) of abaloparatide. This negatively charged oligopeptide has been shown to target raw hydroxyapatite with incredible specificity, while the abaloparatide constitutes a powerful bone anabolic agent known for its role in 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. This technology is particularly applicable to those with osteoporotic hip fractures where a patient's recovery time often means the difference between life and death.

References

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