Orthopedic injuries have comprised roughly 65 percent of all American service member combat-related injuries associated with military conflicts since WWI [1]. More specifically, 26 percent of all extremity injuries treated during Operation Iraqi Freedom and Operation Enduring Freedom involved one or more broken bones [2]. Such fractures may remove the warfighter from service and demand the attention of medical personnel to treat and monitor the injury, and possibly require rehabilitation.

Fractured bones are not only an adverse consequence of combat, they are also common among military recruits during training. Female recruits have a 3.4-21 percent chance of suffering a stress fracture, and male recruits have a 0.9-7.9 percent probability of experiencing the same injury [3]. While fractures may at first seem trivial, they are “estimated [to] cost . . . $34,000 per soldier [4],” amounting to “as much as $100 million annually in medical costs and lost duty time [5].”

Therapies for healing fractured bones rely almost exclusively on mechanical stabilization of the damaged bone (i.e., use of a cast, pin, rod, or plate). In fact, the only Food and Drug Administration (FDA)-approved drug for enhancing fracture repair is a bone anabolic agent that must be applied topically to the fracture surface during surgery. Such a therapy is inappropriate when surgery is not otherwise required. It can only be administered once (i.e., during the brief period when the fracture surface is exposed), cannot be easily adapted for treatment of multiple fractures, and it is never used for therapy of stress fractures. A non-locally induced bone anabolic agent (i.e., a drug that can stimulate rapid bone fracture healing) that will concentrate selectively on the bone fracture surface and induce accelerated bone formation only at the damaged site is needed. Although existing therapies using anabolic agents have been used to target osteoporosis and bone cancers, we published the first paper regarding a systemically administered bone anabolic agent [6, 7].

Recognizing the need for a systemically administered bone fracture-targeted healing agent, we screened a large library of peptides and other molecules for structures that would specifically home to bone fracture surfaces following intravenous or subcutaneous administration (see Figure 1).

After identifying and characterizing approximately eight potent bone fracture-homing peptides, we initiated a second screen of bone anabolic agents (e.g., both bone growth stimulating hormones and cytokines as well as various low molecular weight bone growth-inducing drugs) that when linked to one of our patented bone fracture-homing peptides would promote accelerated fracture repair (see Figure 2). Fortunately, several fracture-targeted bone anabolic drugs met all initial requirements for advancement into large animal studies. That
is, the targeted conjugates were found to:

- reduce the time for fractured femur repair in mice by roughly half
- induce no detectable systemic toxicity at its effective dose
- cause no ectopic bone formation (at either the injection site or elsewhere)
- lead to regeneration of bone at the fracture site that was biomechanically stronger than the contralateral (unbroken) femur
- result in eventual remodeling of the fractured region into normal cortical bone

Although no bone anabolic agent has ever been targeted to a bone fracture surface, all available data suggest that the strategy should work as well in humans as it does in mice. The bone mineral (hydroxyapatite) to which the fracture-targeting peptides bind is identical in mice and humans, and since the fracture process exposes this mineral similarly in both species, their ability to concentrate an attached drug on the fracture surface should be comparable. Moreover, although none of the bone anabolic agents tested have been used systemically in humans for fracture repair, the best performing of these anabolic drugs are all FDA approved for other indications and have demonstrated safety for repeated administration in humans, suggesting that toxicity should not be a major problem during translation of the therapy to humans. If at least one of the targeted bone anabolic agents selected for further development will yield results as promising in humans as in animals, a paradigm-changing method for reducing the down time of an injured warfighter suffering from a broken bone may be achievable.

**REFERENCES**


**BIOGRAPHIES**

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