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Perspective Article

Hylonome

# Introduction – Mechanisms of fracture healing and pharmacologic control

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## Introduction

Approximately 8 million bone fractures occur annually in the United States. Most of these cause interruption of work and activities of daily living, and many are associated with long-term, permanent disability or increased mortality. The majority of skeletal fractures heal normally after fixation. However, approximately 10% of skeletal fractures heal more slowly than normal or fail to heal. These fractures are classified as malunions or non-unions, respectively. Therapies that could enhance and ensure bone healing, accelerate the return of normal musculoskeletal function to an affected individual, and reduce mortality would provide substantial health benefits. Although many innovations in surgical techniques and orthopaedic procedures contribute to this goal of enhancing bone healing, there are currently limited therapeutic interventions to address this medical need.

Significant scientific advances have been made in the area of the molecular basis of bone biology. Scientific breakthroughs have been made in the molecular basis of bone formation and bone resorption. From this new understanding of bone biology, new medicines have emerged for the prevention and treatment of osteoporosis. These new therapies have emerged at a time when osteoporosis has become a major healthcare issue. The US National Osteoporosis Foundation estimates that currently 25 million Americans are affected by osteoporosis and at heightened risk for skeletal fractures including hip fractures. The number of women and men who will suffer from osteoporosis and fractures will rise as the worldwide population greater than 60 years of age increases from about 540 million to more than 1 billion by the year 2020. Even with the emergence of highly efficacious treatments for osteoporosis such as bisphosphonates, fractures are only reduced by about 50%, thus still impacting a large number of people who must suffer from debilitating fractures. Not only are osteoporotic fractures debilitating, they also have a high mortality rate. For example, it has been estimated that about 24% of people over 50 years of age who suffer a hip fracture die within one year of that fracture. Thus, improved therapeutic interventions to speed and insure bone healing are needed.

In spite of significant scientific advances in bone biology, the molecular basis of bone healing in fractured or injured bone is less well understood and advances have not kept pace with other areas of bone biology. As a direct result, pharmacological approaches to enhance bone healing have not kept pace with recently approved therapies for osteoporosis. Emerging science in the area of bone healing is rapidly accelerating and will likely provide new therapeutic strategies and interventions to healing in the years to come.

## The bone healing cascade

The bone healing process via callus formation is divisible into 4 critical phases. The first phase occurs immediately following fracture and involves the formation of a hematoma at the site of bone injury. The second phase is the inflammatory phase where populations of inflammatory cells and cells of other lineages appear at the site of the injured bone and are involved in the release of cytokines and growth factors that initiate the healing process. The third phase involves the formation and mineralization of the callus to bridge the bone defect. The final stage of bone healing involves the replacement of the mineralized callus with mineralized bone and the sculpting of the bone back to its original shape and biomechanical competency via modeling and remodeling.

Each step of the healing process requires a tightly orchestrated sequence of molecular signals in the required cell setting in motion the biological processes. The cascade of molecular signals determines the synchrony of steps in bone healing. Understanding each of these signaling events in the bone healing pathway furthers our ability to intervene in the fracture healing process to rectify inadequate or failed healing. Through the elucidation of the molecular events

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involved in bone healing, new targets of therapeutic intervention will be elucidated. Targets for intervention expands therapeutic options to enhance bone healing or to treat bone defects that have failed to heal.

## Questions to consider from each of the presentations:

1) What are the major gaps in our understanding of bone healing? Where must we focus future research attention? What are the opportunities for collaborations across different disciplines in this area?

2) What are the critical points in the healing cascade that are potential targets of intervention for new therapies?

3) What is the "best" preclinical model of bone healing? Diaphyseal model? Metaphyseal model? Which model best predicts human fracture healing?

4) Are there species differences in bone healing that make some species preferred over others in terms of their relevance to human healing? Example: is the bone healing process in mice, rats, rabbits, dogs, monkeys identical to healing in humans?