From Bench to Bedside

From Bench to Bedside: Targeted Therapy, Denosumab, and 21st Century Orthopaedics: Targets Abound, But Where Are The Therapies?

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Denosumab represents a fully human, monoclonal antibody against receptor activator of

nuclear factor B (RANK) ligand. In layman's terms—or terms more familiar to orthopaedic surgeons not preparing

for a recertification exam—denosumab inhibits osteoclasts, mimicking the natural action of osteoprotegerin. Denosumab has been proven to delay or prevent overt or impending fractures requiring treatment in patients with a wide variety of malignancies [5, 6, 16]. It can be used to treat or prevent osteoporosis [12], and is generally considered as effective in these regards as the late-generation bisphosphonate zoledronic acid. More recently, denosumab has demonstrated efficacy as a standalone or adjuvant therapy in the management of giant cell tumor of bone [2, 3], an aggressive benign tumor that has a proclivity for local recurrence.

Better still, denosumab has, in the past few years, been FDA-approved for the treatment of “unresectable” giant cell tumors [19]. In addition to giving both hope and local inhibition (if not complete control) to patients with this difficult condition, broader clinical use of denosumab in patients with giant cell tumor promises prevention or delay of local recurrence and “downstaging” of surgical disease—making morbid surgery less so and, in some cases, “unresectable” lesions resectable [15].

*A Note from the Editor-In-Chief:
I am pleased to present the next installment of “From Bench to Bedside,” a quarterly column written by Benjamin K. Potter MD. Dr. Potter is a clinician-scientist in the Department of Orthopaedics at Walter Reed National Military Medical Center and in the Department of Surgery at the Uniformed Services University of Health Sciences. His column investigates important developments that are making—or are about to make—the transition from the laboratory to clinical practice, as well as technologies and approaches that have recently made that jump.*

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This is fantastic news. Indeed, in this age of increasingly personalized medicine, it seems one cannot open the paper without reading about some fantastic new antibody, drug, or immunotherapy that will “cure” cancer or “change the world” [4, 14].

As physicians and surgeons, we know better. Even denosumab, for all of its promise, has already demonstrated in its brief time on the market that it (like every new therapy) is not a panacea—failing to completely solve issues ranging from giant cell tumor recurrence [11] to atypical femur fractures classically seen following long-term bisphosphonate use [17].

But the promise—and, on some levels, delivery—of denosumab further highlights a more pressing question, namely: Where are the other targeted therapies in orthopaedics? Rotator cuff tears, degenerative disc disease, and osteoarthritis afflict tens of millions of people in the United States alone—surely there must be some agents on the market (or nearly so) to prevent or treat these vexing problems in “targeted” fashion, right? Or not. Numerous targets have been identified to improve rotator cuff tendon healing [13], and a recent investor’s guide highlighted 17 candidate drugs from 12 companies for the treatment and prevention of degenerative disc disease [10]. But no therapeutic agents are yet available. Likewise, a recent review

identified several targets, new and old, for nonsurgical mitigation of osteoarthritis via so-called disease modifying osteoarthritis drugs and identified the zero drugs available in this hypothetical class [1].

The problem is three-fold—cost, time, and regulations. The Tufts Center for the Study of Drug Development [18] suggests that it costs around USD 2.6 billion and takes more than 10 years to bring a new drug to market. Navigating the FDA-approval process, assuming a candidate drug works, adds additional hurdles and contributes to both the time and expense required. Even the approval of denosumab for treatment of giant cell tumor was granted through a special process (which I applaud) to expedite approval for agents to treat rare or “orphan” conditions. But this sword cuts both ways; osteoarthritis, for example, is not at all rare. The bar is thus much higher for the most common orthopaedic ailments for which such treatments are most needed.

Fortunately, there actually are agents under investigation or “in the pipeline.” Unfortunately, none of the agents appear overwhelmingly promising or close to market at this point. So what to do in the meantime? First, participate in trials and assist with recruitment whenever possible; if interested, one need look no further than clinicaltrials.gov and search for

active trials (lead investigators are listed, as well) within your personal area of interest or expertise. Next, do not worry—when the first big, targeted therapy for osteoarthritis hits, it will not put orthopaedic surgeons out of business. Most importantly, avoid unproven therapies or, worse still, therapies essentially proven ineffective, such as viscosupplementation, arthroscopic lavage for knee osteoarthritis, or porcine small intestine submucosa augmentation of rotator cuff repairs [7–9]. Last, however, might simply be not to kid ourselves that the era of personalized medicine and targeted therapies has yet arrived.

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