Standard Review Article

OPEN

Fracture healing—orthobiologics: from basic science to clinical application

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Summary: Orthopaedics as a field and a profession is fundamentally concerned with the treatment of musculoskeletal disease, in all of its many forms. Our collective understanding of the cellular mechanisms underlying musculoskeletal pathology resulting from injury continues to evolve, opening novel opportunities to develop orthobiologic treatments to improve care. It is a long path to move from an understanding of cellular pathology to development of successful clinical treatment, and this article proposes to discuss some of the challenges to achieving translational therapies in orthopaedics. The article will focus on challenges that clinicians will likely face in seeking to bring promising treatments forward to clinical practice and strategies for improving success in translational efforts.

Key Words: orthobiologics, research, basic science

1. Introduction

This article is organized into 4 specific sections. First, the article will address strategies that young clinicians may consider when making career choices, focusing on considerations for balancing clinical practice and research ambitions when making early career choices. We will further discuss why challenges in translational medicine seem to fail so often and how more specific targeting of basic cellular pathways based on computational modelling and high throughput analysis may ultimately improve successful pathway targeting. Next, the article reviews findings from recent clinical trials in the field and contrasts the sophistication of the medications with limitations in the clinical outcome tools used for demonstrating efficacy. Finally, a brief overview of the FDA process highlights the steps necessary to take a promising orthobiologic treatment through the regulatory process to approval and eventual clinical use.

2. Study Design Tactics That Optimize the Potential for Clinical Translation of Basic Science Research: Hard Learned Lessons

The goal of basic science research is to achieve translation to clinical medicine. Sometimes this goal may be quickly attainable, and other times, it takes several years. The goals of this article were to provide suggestions that will help an early career surgeon or basic science researcher efficiently complete the necessary translational research to turn an idea into a clinical innovation. The easiest way to allow for translation of basic science research to clinical medicine is to efficiently complete this research.

The first and most important step in basic science research is seeking out appropriate mentorship. For any young surgeon, having appropriate career and surgical mentorship is the bedrock of developing a flourishing practice; basic science research is no different. The ideal mentor would be an orthopaedic trauma surgeon at your institution with a basic science research apparatus that is already developed. If such a colleague does not exist, anyone familiar with the hurdles of basic science research can be a valuable resource.

Basic science research is different from clinical research in that you cannot perform it at the same time or in the same location as your clinical practice. Clear communication between you and your employer, and you and your partners, regarding the time commitment away from clinical practice to perform basic science research is mandatory to prevent subsequent confusion, disagreements, and disillusionment.

You need to understand the research strengths of your institution. This will help hone down your basic science research questions. Does your institution have a robust biomechanics laboratory? Do they have a well-developed cell biology apparatus? Using what your institution already has in place will save substantial time in the planning and development phases as you will have to do less groundwork.

When you understand the strengths of your institution, you can start to develop a specific research question. Having a broad area of basic science interest is great because it allows you to tailor your specific questions to what is available to you and your institution. It is important to recognize that translating results from animal models to humans can be a lengthy and unpredictable process. This does not mean that small animal research

The authors declare no conflicts of interest.

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Source of funding: Nil.

The manuscript is exempt from ethical approval/informed consent requirements because it does not involve human or animal subjects.

OTAI (2023) e262

Received: 20 October 2022 / Accepted: 30 December 2022
Published online 4 May 2023

http://dx.doi.org/10.1097/OI9.0000000000000262

should be abandoned, but you do have to be aware that translating it will take some time.

3. Plan Everything

A good plan is a flexible plan, and everyone's plan will change at some point. Dwight Eisenhower once said, "plans are nothing, but planning is everything." One of the biggest parts of planning is budgeting. Many institutions have budgeting offices that help you plan research. Involve them early and often. Be sure to add at least 10% to the proposed total budget amount to account for unexpected cost increases that can occur during this study. Without a budget, no one is going to consider you for grant funding. During budgeting, your plan will likely change multiple times.

As you are planning and budgeting, you must consider staffing. Basic science research requires a team. As your plan complexity increases, the number of people required to execute this plan will increase exponentially, not linearly. You need to consider who you need to help and how they are reimbursed. You also need to consider their schedules. Unless the people helping you are full-time employees paid to work with you, you will need to accommodate multiple schedules while planning, and this is often difficult. You may donate your time for free but do not expect employed professionals working with you to do likewise.

Once you have a team, now you need to determine what training is needed. If you are doing animal research, your team must be trained in animal care as well as any surgical and postsurgical care. Collaborative Institutional Training Initiative (CITI Program) training is required for any research associated with human subjects. Training on biomechanical equipment is needed for anyone helping on a project. Ensuring that this is performed before the project starts will prevent any unnecessary delays and allow for a more rapid completion of your project, which allows for faster clinical translation. While training and planning animal research, you must determine what regulatory agencies need to be aware of your research, including local IRBs all the way to the US Department of Agriculture. Ensuring that all regulatory paperwork is up to date will prevent unnecessary delays or early termination of your project.

Every step in your research plan requires demonstration of prior experience. If you or your laboratory does not have personal experience with procedures or processes that are a part of your project, plan on doing preliminary work to demonstrate your competence to potential funders. If you have not personally performed a part of your project, plan on piloting it ahead of time. Just because someone at your institution has had success does not mean that you will. Pilot data provide important information regarding project timing and feasibility. It will make your plan change. Pilot data can also be publishable and can be used in grant applications. Start small. Little successes lead to big successes. Demonstrating a track record of success in smaller projects will allow for people to have confidence that you can complete larger projects. Be flexible. Your plan will change, you will adapt. Finish your project. The only thing worse than negative results are no results. Do not stop halfway. Finally, tell your colleagues of your successes and your failures. The only thing worse than a project not going how you want is finding out after the fact that someone else had the same issues but did not share them.

4. How Do We Better Target Basic Science Pathways for Clinical, Surgical, and Orthobiologic Modification?

In several studies, we have described some of the recent advancements in the therapeutic targeting of biologic pathways. But even as promising as some of those investigations and clinical studies have been, the overall translational landscape is extremely hostile to seemingly great ideas actually reaching patients. In one estimation, only approximately 10% of the most prominently published basic science mechanistic reports were found to have made it to clinical trials.[1] The authors of this study tested the assumptions that the very best of translatable studies should make it to people to affect health or at least reach the point of testing. When they systematically searched *Science, Nature, Cell, Nature Medicine, Nature Genetics, Nature Immunology*, and *Nature Biotechnology*, they initially found 2000 such "basic science" articles. After application of inclusion and exclusion criteria, they focused on 76 therapeutic options. To their surprise (and perhaps our demise), they found that only 37% of the results were replicated in human trials, 18% were contradicted in the trial setting, and 45%, almost half, remained untested; only 8/76 were actually approved for human use. As a nonorthopaedic but relatable example, ischemic stroke had a cumulative 500 potential therapies based on animal models. At the time of publication of the analysis, the only effective therapeutics were ASA and TPA.

Why does translation fail so frequently? There are likely many reasons including flaws in the animal model of the disease, infidelities in translating the model results to a parallel clinical trial, publication bias especially of negative results, and perhaps most fundamentally, uncertainty of the characteristics of the disease we are actually trying to model and cure. Do we have the requisite understanding of the pathophysiology we are trying to replicate in a model? Again moving from orthopaedics, we likely understand myocardial infarction well enough to model. A little closer to orthopaedics, our understanding of rheumatoid arthritis is reasonable. But do we really understand posttraumatic osteoarthritis after a pilon or plateau fracture? Do we really understand nonunions or unions for that matter? For instance, my collaborators and I recently published the potential effects of Gli protein manipulation and of stimulating Epidermal Growth Factor Receptor signaling to prevent posttraumatic osteoarthritis in murine models.[2,3] Hence, targeting of hedgehog protein and Epidermal Growth Factor Receptor pathways should be highly translatable, correct?

We hope so, but we just do not know with high fidelity. The true fidelity of our murine model, Destabilization of the Medial Meniscus, despite being one of the best models we have to predict human disease, is not yet rigorously understood. To translate cell and molecular therapies to the clinical setting, we need a much more sophisticated cell and molecular understanding of what happens in normal fracture healing, how that breaks down in delayed healing, and how that can be mitigated. We need detailed natural history studies that combine patient-oriented phenotypes (objective and subjective) with molecular profiling at the tissue, cell, and molecular (gene to expression) levels. We also need to better understand how pathways, often treated as being linear or 2 dimensional, interact to influence each other to amplify, dampen, and modify each other; fundamental bone cell signaling pathways Notch and Wnt do not exist in isolation, they interact and coregulate.[4] Although it might not be the final answer, computational analysis of complex cell and molecular interactions using the power of high throughput single cell (or nuclear) RNA sequencing is an example of how we may be able to better understand complex in situ interactive systems including previously unknown cell populations and function.[5] Such a spatiotemporal understanding of normal and abnormal biology of the dynamic system will allow for more precise and useful targeting for therapeutic effect.

5. From Basic Science to Clinical Application

Our collective understanding of the molecular biology driving fracture repair and skeletal regeneration has grown exponentially in recent decades. Because more sophisticated laboratory techniques have emerged, a growing understanding of mechanotransduction, autocrine and paracrine cellular signaling, and stem cell differentiation is emerging. This has opened up new avenues of investigation and new targets for potential therapeutic approaches to enhance fracture repair and reduce rates of fracture nonunion.

Despite a more sophisticated understanding of the cellular mechanisms that drive both endochondral ossification and intramembranous bone formation, actual clinical tools for harnessing this knowledge and translating it into improved clinical outcomes have proven elusive. Fracture healing is, after all, surprisingly robust, and improving on a largely successful process is itself a challenge. Our tools for measuring rates of fracture repair are also fairly blunt instruments, which may also hamper these efforts.

The Wnt signaling pathways are well-known regulators of fracture repair.[6] The secreted frizzled-related protein, Dikkofps, and sclerostin proteins all modulate Wnt signaling. In general, increased Wnt signaling has led to more robust fracture repair.[7,8] To this end, investigators have proposed a variety of methods for applying this effect clinically. Monoclonal antibody treatment, which has had dramatic effect in the treatment of rheumatoid disease and other auto immune disorders, is clinically in use for treatment of osteoporosis.[9,10] Antisclerostin antibody therapy was also shown to enhance fracture repair in various animal models.[11–13] Yet recent large scale clinical trials in humans have failed to demonstrate this effect in humans. In a recent trial, 332 patients with hip fracture were randomized to romosozumab or placebo, and no effect was seen on radiographic scoring or timed up and go studies. Similarly, 400 patients with diaphyseal tibia fractures were randomized to romosozumab or placebo, with no effect seen on radiographic union scores or functional scoring.[14,15]

The inability of the trials to demonstrate effectiveness may simply be that the effect of the drug is too small to be clinically relevant, particularly in fractures which would otherwise heal uneventfully. However, a radiographic scoring measure such as the RUST[16] or the RUSH[17] scores of radiographic union may also be too crude of a tool to detect the effect of any drug, particularly in combination with rigid and robust internal fixation devices. Furthermore, the inherent limitations of the radiographic scoring systems require large numbers of patients to be enrolled to power these studies sufficiently, and another limitation in translating basic science advances to clinical use.

Antisclerostin antibody treatment initially found success in treatment in osteoporosis and was then tested for its effect in fracture repair. Other drugs may follow a similar approach. Recent clinical trials of drugs for treating anemia associated with renal failure also hold promise for enhancing fracture repair. The Hypoxic Inducible Factor is a key regulator of cellular response to hypoxia and a known driver of chondrocyte behavior.[18] Inhibitors of prolyl hydroxylase are in trial for treatment of chronic anemia; this drug class targets the hydroxylase and allows for intracellular Hypoxic Inducible Factor to accumulate. After translocation to the nucleus, this increases production of a number of provascular proteins, including VEGF. Its positive effect on fracture repair in animals has been demonstrated.[19] Although this class of prolyl-hydroxylase inhibitors may be effective in enhancing fracture repair, whether the effects will be enough to overcome our current limitations in clinically measuring rates of fracture repair remain to be seen.

6. Translational Challenges in Fracture Repair: Navigating the FDA Approval Process for New Devices

The orthopaedic surgeon can be in the position of participating in the development of new devices—devices that will require FDA approval before introduction to the marketplace. Navigating the myriad pathways and nuances involved in FDA approval can seem a daunting task.[1,2,20,21] Until recently, there were 2 FDA pathways by which to seek approval for a new device: the premarket notification pathway (PMN) and the premarket application pathway (PMA). In a 2017 guidance document,[3] the FDA added a third pathway, the DeNovo device (DD) pathway, intended to speed the approval of devices with demonstrated safety and effectiveness, but involving new technology.[22] This guidance was further updated in 2019.[4] This overview will describe each pathway briefly and then provide a perspective on how to engage with the FDA regarding an application for device approval.

The PMN pathway (more commonly known as the "510 K pathway") involves the applicant making a case to the FDA that the new device is largely equivalent to a "predicate device" that already has FDA approval. In considering a PMN application, the FDA may require laboratory or clinical data (usually a case series is adequate) to help support the case. The PMN pathway is the simplest, fastest, and least expensive of the 3 pathways; for these reasons, it is often the first pathway sought by an applicant. Increasingly, however, the FDA is reluctant to grant PMN approval for new devices, causing applicants to pursue one of the other pathways.

The PMA pathway is the longest and most expensive of the 3 pathways. This pathway often requires prospective clinical data (often a randomized controlled trial) before the FDA will consider the application. This "investigational device exemption" (IDE) study allows the device to be used only for the generation of data to support a PMA application for the device. The entire length of time from the beginning of IDE study planning until FDA approval (if the FDA approves) can easily span 7 years.

In guidance published by the FDA in 2017,[3,4] the FDA established a DD pathway for approval.[23] A device may be permitted to follow the DD pathway if (1) there is no approved predicate device (the new device fails to meet the 510 K standard) and (2) the applicant can demonstrate there are substantial existing data to substantiate safety and effectiveness. The DD pathway can be nearly as rapid as the PMN pathway, provided that substantial data exist and the FDA finds the data compelling. In fact, the FDA, by rule, must render a determination within 100 days of the time a DD application is made.

How is an applicant to choose a pathway? The FDA provides for applicants a variety of presubmission interactions[5]; it is in these interactions that the applicant can educate the FDA about the new device, present data and arguments supporting the device's safety, and receive feedback and guidance from the FDA as to what pathway is most appropriate.[24] Applicants should take advantage of these interactions for it is in these presubmission discussions that the applicant and the FDA can have dialogue and come to agreement on what data exist, what additional data are needed, and what pathway is appropriate. Furthermore, these interactions are where the details of an IDE study (if needed) are worked out. The FDA does not limit the number of presubmission interactions an applicant can have, and applicants should take advantage of this. Applicants should approach these meetings as a series of dialogues, where both parties present information and

opinions. Over a series of such meetings, conversations will lead, ultimately, to agreement on what pathway is most appropriate and what additional data (including an IDE) are most beneficial to an application.

Navigating the processes for FDA approval of a new device can seem complex and daunting. The recommended strategy is to first consider the possibility of PMN approval, followed by DD approval, and then PMA approval only if the first 2 are not possible. It is strongly recommended to pursue these strategies by taking full advantage of presubmission interactions with the FDA; these interactions should be approached as a series of conversations, the goal of which is to educate the FDA about the new device, make them familiar with existing published data substantiating the safety and effectiveness of the device, and ultimately to reach mutual agreement on what is the most appropriate pathway to pursue for approval of the new device. As orthopaedic surgeons, we most commonly think of the FDA as an entity that "approves or rejects"; however, in this case, they are best approached before submission as a group that one can have dialogue with and reach agreement on the best approach for the new device.

7. Conclusions

Despite our burgeoning understanding of musculoskeletal cellular pathways and the rapid expansion of tools and techniques that basic scientists have at their disposal, translation to clinically efficacious treatments is rarely successful and never easy. Understanding these challenges, both in the clinical workplace and in the laboratory, can facilitate this work. The use of specific tools such as high throughput RNA analysis may focus researchers onto more successful potential treatments. Reviewing challenges faced by recent translation studies can inform future work, and having a thorough understanding of regulatory pathways is crucial for those clinicians who hope to champion successful translational research.

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