Chapter 1
Introduction to Regenerative Medicine

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Regenerative Medicine Intro Combined

Patients suffering from musculoskeletal ailments frequently seek additional treatment options after more traditional methods have failed. Though eager for alternative methods, they may have reservations over the safety and efficacy of the broad range of regenerative medicine techniques, which can make regenerative medicine a somewhat controversial topic [1, 2]. A large pool of anecdotal evidence exists, but there is no standardization of techniques, and evidence-based research has strained to catch up (Table 1.1). As is the case with cutting-edge treatments, research is continually emerging. By reviewing, evaluating, and exploring the current state of regenerative medicine research, we hope to provide a foundation upon which the practitioner can converse with the patient. Organizing the book based on the anatomic site of injury will allow the medical practitioner to easily reference evidence-based regenerative medicine treatment options and help guide open discussion with their patients about additional treatments that may be appropriate to offer.

In the broad sense of the term, "regenerative medicine" is delivering cells or products to diseased tissues or organs in the attempt to restore tissue or organ function. What we are interested in is connective tissue and bone regeneration [3]. The rationale for using these therapies is that the injected product will stimulate repair of these damaged structures as opposed to only treating the patient's symptoms. To understand these regenerative options, it is important to look back at the history of platelet-rich plasma (PRP) and stem cell therapy.

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G. Cooper et al. (eds.), *Regenerative Medicine for Spine and Joint Pain*,
https://doi.org/10.1007/978-3-030-42771-9_1

Table 1.1 Regenerative Medicine Questions

What is the particular "injectate"?
Are we using leukocyte-reduced or leukocyte-enriched PRP?
How are you harvesting your stem cells?
Bone marrow aspirate, bone marrow concentrate, or mesenchymal from adipose tissue?
What about embryonic products?
Which therapy is the most powerful "regenerator"?
How do we price them?
How much volume is just right for your patient?
Do they need a single or series of multiple injections?
If we are treating an arthritic condition, then what stage of arthritis responds best?
How active is the patient?/What level of competition?
Gender?
What is the post-injection rehabilitation protocol?
As you can see, there are many possible combinations of answers to the above questions, which makes this field very intimidating to patients and practitioners because of the many variables.

Platelet-rich plasma was developed in the field of hematology in the 1970s [4]. PRP releases growth factors, which are also known as bioactive proteins. These proteins aid in stimulating the body's natural ability to heal. Hematologists were treating thrombocytopenia with a product that was plasma with a platelet count higher than peripheral blood. In the late 1980s, it was used during open heart surgery. Then, in the 1990s, maxillofacial surgeons were using PRP to aid in healing skin flaps. Next, it was used in musculoskeletal medicine. The first documented case in *Sports Medicine* was in 1999, when Dr. Allan Mishra used PRP to treat San Francisco 49ers quarterback Steve Bono's Achilles tendon injury. In 2006, PRP use for elbow tendonitis was published in the *American Journal of Sports Medicine*. That study showed 60% improvement in pain levels immediately, 81% improvement in 6 months, and 93% improvement at 2 years. This is when PRP gained significant popularity and many well-known professional athletes began using PRP therapy including Kobe Bryant and Tiger Woods [5]. It then gained popularity among orthopedic surgeons for treating fracture nonunion, arthritis, tendonitis, muscle strains, cartilage injuries, and more [6]. Today, PRP is being used in pediatric surgery, gynecology, urology, plastic surgery, dermatology, and ophthalmology.

Stem cells are cells that have the ability to differentiate or change into a particular cell. A specific type of stem cell known as a mesenchymal stem cell can transform into a bone, cartilage, muscle, or fat cell. The first scientists who defined the key properties of stem cells were Ernest McCulloch and James Till in the 1960s. They discovered that the cells can divide and differentiate into mature cell types [7]. Then, in 1996, scientists were crossing ethical boundaries when attempting to clone "Dolly the sheep" by using stem cells. In the early 2000s, Dr. Shinya Yamanaka discovered skin cells can be converted into stem cells by altering gene expression. This was the birth of induced pluripotent stem cells, or iPS. Since then, stem cells have been used in musculoskeletal medicine and many other areas including gene therapy for inheritable disorders.

As you will find, the research is not unambiguous. Patients who have been failed by more traditional treatment options are frequently desperate for additional potential treatments. Demand for regenerative medicine is growing as the amount of evidence increases. Oftentimes, patients are initiating the conversation about regenerative medicine and it is important for the physician to be well prepared for such a discussion. Practitioners must be ready to acknowledge the lack of clear-cut evidence at times and be open to frank discussions regarding the risks of treatment and potential benefits [8]. Informed consent is paramount and cannot be stressed enough. The ability to counsel on the risks and benefits of different regenerative medicine techniques based on the current literature is the first step to offering regenerative medicine treatment options. Though it is important to remain hopeful that regenerative treatment will allow for improvements when more conservative measures have failed, it is essential to develop realistic goals with the patient.

As the number of degenerative and chronic conditions continues to climb among the population, demand for regenerative medicine is increasing. Regenerative medicine and tissue engineering have been identified as top research priorities by the Medical Research Council in the United Kingdom and the National Research Council of the United States [9]. With increased interest and research into regenerative medicine, the ambition to transition healthcare from a focus on symptomatic treatment to a more curative treatment approach grows [10]. Because of this growing expectation, significant controversies exist. Concerns include research misconduct and tumor development [11, 12], while unproven therapies are creating an entire stem cell tourism industry with little safety oversight for patients desperate for therapeutic treatment [13]. In addition, there are multiple manufacturers of the systems that isolate the injectate, so not every physician offering regenerative medicine is using the same concentration of growth factors. Another major barrier to administering regenerative medicine to patients is that insurance companies generally do not cover these injections. It is difficult to say if the Food and Drug Administration (FDA) could administer an approval since "the injectate" is not a product of a pharmaceutical laboratory, but it stems from the patient themselves. Despite these obstacles, regenerative medicine continues to make progress with regard to safety and its use of evidence-based treatment options. As the number of clinical trials continue to increase, regenerative medicine is at the cutting edge of translational research and will require a collaborative effort among a vast array of interdisciplinary researchers and clinicians [14]. This further cements the need for an evidence-based, practitioner-friendly guide to regenerative treatments.

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