

Preface

Over the past century, the human life span has almost doubled owing to technological advancements. Thanks to modern medications, sterile techniques, antibiotics, and preventive health care, people are living longer, and critical health issues have changed from infectious epidemics to diseases associated with aging. Today, chronic illnesses top the list of the causes of morbidity and mortality in almost every country: cardiovascular diseases, diabetes, cancer, and neurodegenerative disorders. This paradigm shift has created new challenges and calls for new treatments. Symptomatic therapies and temporary relief for chronic illness can no longer accommodate the expanding needs of an aging population and the extended life span that older people now enjoy without providing similarly enjoyable healthy living. This has created a need for new therapies that aim at curing chronic diseases and not just palliating them. It was thus inevitable that stem cell research would gain substantial momentum since it was first discovered that stem cells could save lives following lethal irradiation.

The first modern bone marrow transplant was performed in the 1950s. Unlike blood transfusions, which failed to save victims of nuclear accidents, cells in marrow transplants seem to have the capacity to sustain the production of blood cells. These cells were dubbed *hematopoietic stem cells* (HSCs). To date, HSCs are the most and best researched and characterized cells. A vast array of specialized equipment is now available on the market that can be used to purify HSCs to a clinical grade for direct infusion into patients. Diseases now routinely curable by HSC transplantation include leukemia, lymphomas, multiple myeloma, and many disorders of the blood and lymphoid tissue. Many clinical trials have also shown promising therapy for solid organ diseases, such as breast cancer and autoimmune diseases. However, HSC transplantation is a complex and expensive procedure that puts patients, who must endure long absences from work and prolonged recovery issues, under significant physical and financial stress. Furthermore, HSC transplantation entails a long search for a matched donor and significant perioperative immune suppression, causing significant perioperative issues and higher morbidity and mortality. These challenges regarding the consistency and safety of treatment begged for alternative cells that would bring better therapeutic outcomes.

Within the bone marrow lies another population of stem cells, characterized by multilineage differentiation into stromal cells such as fibroblasts, bone, fat, and cartilage cells. These are called *mesenchymal stromal cells* (MSCs) (or, more commonly and less accurately, mesenchymal stem cells). MSCs have quickly gained popularity over HSCs and became the preferred cells for the treatment of nonhematopoietic disorders, for several reasons. Mainly, MSCs are easy to culture and relatively safe and offer a low-cost transplantation procedure. MSCs were first obtained from the bone marrow and then from other tissues, including umbilical cord, placenta, and adipose tissue. Today, we can collect MSCs from almost any tissue in the body. They can be expanded with relative ease, as plastic adherent cells, to large numbers, based on patient needs. They can be autologous or allogeneic, but because of their low immunogenicity and favorable immune functions, especially their immune suppressive qualities, they have some advantages in terms of transplant procedures. In this regard, they are considered safer than HSC transplantation, which necessitates the vigorous immune suppression of often already debilitated patients. Because of the ease of their culture and expansion, they are also the preferred candidates for scaffolds, for purposes of tissue and organ engineering. Plausibly, there has been a surge of clinical trials that have disproportionately favored MSCs.

Surveying the several thousand publications and clinical trials using stem cell therapy—hematopoietic disorders aside—MSCs appear to be the most utilized stem cells in experimental transplantation. In many of these experiments and trials, MSCs are transplanted without prior differentiation into the desired cell population. Nevertheless, reports on improvements in the symptoms and signs of recovery are consistent. Many scientists argue that the efficacy of MSCs is not attributable to their multipotency or contribution to the reconstitution of the damaged tissue by replacing diseased cells with healthy ones. Rather, they work because of paracrine or immune-modulating effects, which improve the microenvironment of the affected organ and promote growth factors and endogenous stem cells. New technologies and tracking methodologies will help provide a better understanding of the mechanism of restructuring a diseased tissue following stem cell treatment. Whether infused stem cells contribute to restructuring damaged tissue, which was initially thought to be the ultimate target of stem cell therapy, remains to be verified.

Recently, sporadic clinical trials using embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) started in centers mainly in Asia and the USA. Although these efforts are not covered in this book, much hope rests on such trials. ESCs are considered “de facto” stem cells. They can robustly differentiate into cells of multiple lineages both in vitro and in vivo. When injected into animal models, they form teratomas, composed of a mixture of tissues that correspond to all lineages. They have longer telomeres and express embryonic genes. Among all types of stem cells, ESCs have a unique flexibility and unmatched capacity for differentiation into the desired cell populations. However, many issues need to be overcome before ESC use becomes a reality in routine clinical settings. For example, the reliability and sustainability of the differentiated cell type remain issues as does the safety of transplanted cells. Ethical considerations have also hampered ESC research, although restrictions are being relaxed in several countries in response to

public awareness and strict regulations. Much anxiety over ESC research has been relieved with the introduction of iPSCs.

Indeed, since the first cloning of frogs by Gurdon and colleagues in the fifties, and later, the famous sheep Dolly in the nineties, it has become apparent that our understanding of biology, embryology, and organ formation has been severely deficient. It also became apparent that cell manipulations by chemicals or additives could change cells in fundamental ways not considered previously. Yamanaka's work, which won him the 2012 Nobel Prize in Physiology or Medicine, achieved what many had only dreamed of: changing somatic cells into ESC-like cells. Using four transcription factors, Yamanaka's group induced pluripotency in an adult fibroblast. No longer should the scientific community endure the controversies of using ESCs. This technique, however, is still far from perfect. Some of the transcription factors used to induce pluripotency were oncogenic and could stimulate tumorigenesis. Many ongoing efforts are improving the safety of iPSCs; however, issues with the reliability of differentiation and long-term safety remain unresolved.

Where do we stand now, and is the use of stem cells for the treatment of non-hematopoietic disorders close to being a reality? The answer to this question varies depending on many factors. Our group has recently a meta-analyses to evaluate the use of stem cells in the treatment of diabetes mellitus. It was interesting to find that among the 4000+ studies that appeared in response to the key words "diabetes" and "stem cells," only 22 trials were eligible for inclusion in our study on using stem cell transplantation for the treatment of uncomplicated diabetes. The discrepancy between the benchtop and bedside is indeed significant. This analysis led to several conclusions, most importantly, that systematic, well-controlled clinical trials are severely lacking in the area of treatment of diabetes using adult stem cells. It is not unreasonable to generalize this finding and extend it to other applications of stem cell therapy for cardiovascular diseases, neurodegenerative disorders, and urogenital diseases. Our study showed that the type of stem cell, the source of the cells, the route of administration, and dose all contribute to the outcome of stem cell therapy. Patient-related factors that supported a more favorable outcome included earlier intervention, lack of complications, and overall health of the treated patient. Universal conclusions from our study and others reveal the critical need for fine-tuning of stem cell therapy in a much better and more systematic approach than the current practice. This fine-tuning, which encompasses factors related to the diseases, stem cell transplant ation, conditioning protocol, and patient will all ultimately determine the success or failure of the transplant.

The prevalence of diseases of aging, the lack of satisfactory therapy for today's many intractable illnesses, and the anxiety experienced by patients and their families over finding a cure have all driven stem cell research onto a fast, not well-controlled track. As a result, much hype has diluted efforts to systematically design clinical trials and critically evaluate outcomes. Embarking on writing this book at this time is thus an attempt to provide an overview of a work in early progress. Some of the clinical trials covered here are mature, and data are available in large, reproducible outcomes to be recommended for patients on a routine basis. On the other hand, many tissue and organ engineering efforts, as well as utilization of ESCs and

iPSCs, are still almost exclusively experimental, and results are too preliminary to recommend for routine practice. Technological advances in the fields of nanotechnology and material science should, however, accelerate stem cell therapy at unprecedented rates. These technologies should allow for advances in studying the biology of stem cells and enhancing their application in vitro, for both diagnostic and therapeutic purposes. The book covers some of those promising technologies and how they impact the study of biology in general and stem cells in particular. We expect that next-generation stem cells will be those which have been studied and manipulated using technologies that are just being developed and will revolutionize their applications in the very near future.

6th of October City, Giza, Egypt

Nagwa El-Badri

Advances in Stem Cell Therapy

Bench to Bedside

El-Badri Abdelkodous, N. (Ed.)

2017, XVI, 310 p. 31 illus., 29 illus. in color., Hardcover

ISBN: 978-3-319-29147-5

A product of Humana Press