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The exciting prospects of new therapies with mesenchymal stromal cells

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Abstract

From the outset, it was apparent that developing new therapies with mesenchymal stem/stromal cells (MSCs) was not a simple or easy task. Among the earliest experiments was administration of MSCs from normal mice to transgenic mice that developed brittle bones because they expressed a mutated gene for type 1 collagen isolated from a patient with osteogenesis imperfecta. The results prompted a clinical trial of MSCs in patients with severe osteogenesis imperfecta. Subsequent work by large numbers of scientists and clinicians has established that, with minor exceptions, MSCs do not engraft or differentiate to a large extent *in vivo*. Instead the cells produce beneficial effects in a large number of animal models and some clinical trials by secreting paracrine factors and extracellular vesicles in a "hit and run" scenario. The field faces a number of challenges, but the results indicate that we are on the way to effective therapies for millions of patients who suffer from devastating diseases.

Introduction

I was doing research for many years before I realized a simple truth: no matter how hard I tried, there was only a small group of scientists in the world who understood whether what I had done was a small step or a big step in advancing the field. Therefore, this award from my peers in the field of cell therapy has special meaning to me.

By way of background, I might mention that I came into the field of cell therapy by an unusual path. I had gone to medical school and had 1 year of hospital training. I then went to the US National Institutes of Health (NIH) under a program that surprisingly allowed me to do research instead of serving in the military. While at NIH, I was able to complete a PhD degree for research on collagen biosynthesis. What followed was 30 happy years doing research on much the same topic. They were happy years because with experimental tools that seem childishly simple today, we and others in the field were able to unravel the complex pathway by which cells assembled the precursor molecule procollagen and then processed it by seven different enzymes to collagen fibers [1]. While defining the pathway, we searched for drugs that might inhibit the excess deposition of collagen in scars. One series of the drugs, unexpectedly, inhibited degradation of hypoxia induced factor (HIF) and are currently being developed for the therapy of anemias [2]. They were also happy years because I was privileged to work with a group of exciting graduate students and postdoctoral fellows, many of whom went on to outstanding scientific careers and thereby became the most important products of my laboratory. Then there were some unexpected developments. My laboratory isolated the first genes for human collagens [1]. They had fascinating structures but after "cloning and moaning" for several years, we began to wonder what else we could do with them. Fortuitously, we and our competitors at the time discovered that the collagen genes harbored mutations that caused a large family of genetic diseases of bone and cartilage. And after we had identified well over 50 such mutations, we were faced with the next question: what could we do for children such as those who had collagen mutations causing severely brittle bones, the genetic disease of osteogenesis imperfect (OI)? Or what could we do for their parents who were devastated by experiences such as breaking an arm or leg when lifting their child from a crib as

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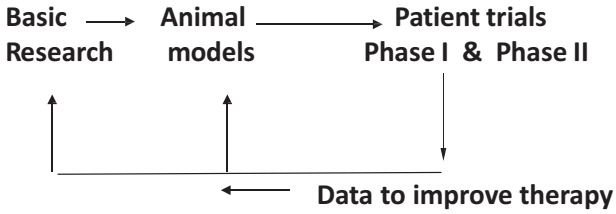

Figure 1. Schematic to illustrate that development of a new therapy is frequently non-linear. The basic research that generates the idea is rarely entirely convincing. The tests of the therapy in animal models leave much to be desired, particularly because rodents repair tissues better than patients. Then, carefully designed clinical trials are required to return to and improve the research so as to produce an effective and safe therapy.

carefully as they could? One of the few answers seemed to be therapy with cells that could differentiate into bone, cells like mesenchymal stem/stromal cells (MSCs).

I mention all this to illustrate that I came into the field of cell therapy with some strengths as a scientist but also some glaring weaknesses. Therefore, I needed to learn, and to keep learning, from members of this Society and others who knew and still know far more than I about hematology, organ transplants, cell biology, immunology and many other topics.

When we and others began working with potential therapies with MSCs, we knew the journey would not be a short or easy one. Also, we knew that hard facts would be much more difficult to extract than in research on the biosynthesis of collagen or mutations in collagen genes. However, we were reassured by the history of most new therapies in medicine. As is well recognized, the process was rarely a linear one (Figure 1). The basic research that first suggested the idea was rarely as convincing as one would like. The initial trials in animal models left much to be desired. With MSCs, the experiments were particularly challenging because they were designed to reduce injury and improve repair of tissues, but rodents that provided the most accessible models healed injured tissues much more readily than patients. In the end, data from carefully designed clinical trials were essential to return to and improve the basic research and the animal models so as to provide new therapies that were both effective and safe for patients. The history of such non-linear developments of medical therapies is a long one. It includes an example very familiar to members of this Society: the 50-year long dialogue between basic science and clinical trials [3] that now provides successful therapies with hematopoietic stem cells for thousands of patients each year. But in testing the therapeutic potentials of MSCs, we were targeting not one organ or tissue but many. Therefore, we were entering a vast new field of cell therapy whose limits were still unknown.

At the time we entered the field in the mid-1990s, there was already a rich literature on MSCs. Beginning in the late 1960s and early 1970s, Friedenstein and others called attention to the cells from bone marrow that adhered to hydrophilic tissue culture surfaces and were spindle-shaped like the cells that provided the stromal support for hematopoietic cells in marrow [4–6]. Over the next 20 or so years, Friedenstein and a large number of other investigators demonstrated that the cells had several attractive features, including rapid expansion in culture, an ability to generate single-cell derived colonies and ready differentiation to mineralized cells, chondrocytes and adipocytes both in culture and in capsules *in vivo*. Most importantly, research on MSCs also demonstrated that the cells served as excellent feeder layers for cultures of hematopoietic cells [7]. This literature was the basis of an experiment we carried out with a line of transgenic mice [8] we had prepared in the course of our research on OI. The mice over-expressed an internally deleted gene for type 1 collagen that we had isolated from fibroblasts of a patient who died due to a lethal form of OI. As expected, the mice developed brittle bones and multiple fractures. The experiment consisted of infusion of MSCs from normal mice of the same strain into the transgenic mice. The results were not dramatic, but the recipient mice demonstrated significant improvements in mechanical tests for bone strength, increases in bone collagen and increases in bone calcium. Also, crude assays we developed before more refined technologies were available suggested that the donor MSCs had engrafted into multiple tissues.

The results we obtained with MSCs in the transgenic mice persuaded Malcolm Brenner to ask Ed Horwitz to join his research group and carry out a trial of MSCs in patients with severe OI [9]. The trial was complex in that the patients first underwent marrow ablation and a bone marrow transplant from a matched sibling or matched potential donor so that they acquired the immune system of the donor. Four or so years later they received MSCs from the same donors. Four of 5 children in the initial cohort began to grow, whereas they had stopped growing before the treatment. Also, they were able to sit up and stand with support for the first time. Most importantly, there were no adverse effects, a result consistent with an earlier trial in which autologous MSCs were infused into cancer patients in remission [10]. However, the beneficial effects in the children persisted for only a few months.

The trial in the patients with OI was based on the hypothesis that the donor's normal MSCs might engraft into sites of recent fractures, differentiate into osteoblasts, and produce an adequate amount of normal type 1 collagen to improve the strength of the patient's bones. The results in the transgenic mice, the patients with OI, and other observations that we and others were making [11–17] returned attention to an