



ISCT TALKING WITH GIANTS

“There may be other fields as exciting and rewarding to work in, but I have trouble thinking of them.”

International Society
ISCT
Cell & Gene Therapy®

5 Questions with Dr. Darwin J. Prockop, MD, PhD

Dr. Darwin Prockop’s long and distinguished career in cell and gene therapy began as a bright-eyed university student at Haverford College in Pennsylvania. There, he completed an undergraduate degree in 1951 and then completed a master’s degree in animal physiology from Brasenose College in Oxford. He earned a medical degree from the University of Pennsylvania in 1956 and a Ph.D. in biochemistry in 1961 from George Washington University. Since then, Dr. Prockop has been a faculty member at the University of Pennsylvania, the University of Medicine and Dentistry of New Jersey, Jefferson Medical College, Hahnemann/Drexel Medical School, Tulane University, and Texas A&M University.

Dr. Prockop’s research as a world-renowned biochemist has focused on collagen and connective tissue diseases. In 2001, he organized the first scientific meeting focused on mesenchymal stem cells (MSCs) – he was ahead of his time. He was elected to the National Academy of Sciences in 1991, to the National Academy of Medicine in 1992, and to the National Academy of Inventors in 2015. He has received two distinguished alumnus awards and three honorary degrees. In 2016, he received the inaugural Career Achievement Award from the International Society for Cellular Therapy.

The pioneering cell researcher sat down with ISCT to talk about how cell and gene therapy field has evolved over the years, where it will be in five years and what his advice is for those just entering the field.

1 How is the cell and gene therapy field different now compared to when you started more than 60 years ago? How has it evolved?

The differences are so great that it’s difficult to describe them adequately. Perhaps two examples from my own experience will help. When we first decided to

study MSCs, we had to invent our own markers for the cells. Luckily, we had just prepared transgenic mice that developed fragile bones because they expressed a mutated collagen gene similar to the mutated collagen genes that produced osteogenesis imperfecta in patients. So we used the mutated collagen gene as a marker for the MSC-like cells we isolated from the transgenic mice. Then we had to invent our own semi-quantitative PCR assay for the mutated collagen gene to follow the distribution of the cells after they were infused into naïve mice. For reasons that were not apparent until later, our PCR assay over-estimated the extent of engraftment of MSCs but the results stimulated more definitive experiments when better assays became available. Today of course, each of us is like a child visiting a candy shop with a dazzling array of methods for marking cells, tracking them and characterizing them with an alphabet soup of –omics. (Laughs) A second example is the time it took me to write my first review about MSCs. The literature was scant but it took me several months to assemble the relevant publications. I worked the stacks of a local medical library and then wrote for help from larger libraries in this country and abroad. Now of course, it would take just a few clicks of a computer mouse.

The result of these and other differences is that journals are now filled with papers we could only dream of – beautiful stories of cell and gene therapy that document for us the effects at the molecular level, in cells, in animal models, and sometimes in patients.

2 Where do you see the cell and gene therapy field in 5 years? Where do you see it headed?

I think both cell and gene therapies will be in the clinic, enhancing the lives of people with diseases that are now incurable. Can there be any doubt after considering the progress of the last five years?

We may be fairly close to gene therapies that can cure or alleviate most genetic diseases that are caused primarily by mutations in single genes like hemoglobopathes, hemophilia, cystic fibrosis, Marfan syndrome and osteogenesis imperfecta. But a limited number of patients are candidates for the therapy because the diseases are rare and there are more practical methods for treating or preventing them in many societies, such as the screening of potential parents of recessive diseases. Also, the therapies may have long-term effects that cannot be anticipated.

Therapies are perhaps achievable for more common diseases like cancers and Alzheimer’s disease. It’s difficult, of course, to predict which of the multiple strategies currently pursued will be the most successful. My own bias is that trials with cells such as MSCs will pave the way since experiments in animal models have demonstrated that they can suppress the excessive inflammatory and immune reactions that make key contributions to the pathology of most chronic diseases. A variation on this strategy is to use as therapy the small vesicles (exosomes) that MSCs and other cells secrete and that account for many of their therapeutic effects. Another possibility for a cell therapy is replacing the disease-damaged stem cells in brain and other tissues with a modification or genetic engineering of cells such induced pluripotent stem cells. A cadre of extremely talented scientists are currently pursuing these and other cell therapies. So who can be pessimistic about what we will find in the next 5 years?

3 Why are you so passionate about working in the cell and gene therapy field?

There may be other fields as exciting and rewarding to work in, but I have trouble thinking of them. We are learning the secrets of biology and of life itself. Some of the secrets will help alleviate the suffering of people

who share this planet with us. Some, in ways we cannot fully foresee, may help us save the planet itself.

4 What are the biggest challenges facing the development of new cell and gene therapies?

For cell therapies, assays that are quantitative and real-time for thoroughly characterizing cells and predicting their response to stimuli. We need to know not just the status of a cell at a given time. We need to know its potential for change. And we need to know the changes in the same time-scale that a cell initiates its responses, in nanoseconds or less.

For therapies with extracellular vesicles, including exosomes, far better technologies for isolating them and selecting or engineering them for desirable therapeutic properties.

For gene therapies, adequate precautions for off-target mutations and adequate considerations for adverse effects for the patients and society.

These are not trivial challenges but who can be pessimistic of what we can accomplish in the next 5 years?

5 For young people just starting out in this field now, what would be the one piece of advice you would give them based on your wealth of experience?

I hope you will have a chance to experience the sheer joy of working at the cutting-edge of human knowledge about biology and medicine in spite of the tremendous pressures being placed on young scientists today. It is such a gratifying field and I have met so many wonderful people over the years. But please try to develop as broad and deep an understanding of all of science as you can. You will need it.