ISCT TALKING WITH GIANTS

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International Society ISCT Cell & Gene Therapy®

5 Questions with Hal E. Broxmeyer, PhD

This is a shortened version of the interview. Please visit www.isctglobal.org to read the full interview with Dr. Broxmeyer.

Patients around the world can thank Hal Broxmeyer, PhD for saving their lives. His work helped found and nurture the field of clinical cord blood transplantation, establishing human cord blood as a source of transplantable hematopoietic stem cells. With a team of clinical investigators, his research translated to thousands of cord blood transplants, saving patients with life-threatening malignant and non-malignant diseases. He is Distinguished Professor, Mary Margaret Walther Professor Emeritus, and Professor of Microbiology and Immunology (full time) at the Indiana University School of Medicine. He received a PhD from New York University, then did post-doctoral training at Kingston General Hospital, Queens University Kingston, Ontario, Canada. He worked at Memorial Sloan Kettering Cancer Center (MSKCC) in NYC working up from the rank of Associate Researcher to Associate Member. To date, he has published 795 scientific papers which have been cited 62,800 times with an h-factor of 119/i10 index of 575 (Google Scholar).

Dr. Broxmeyer has been recognized with a number of honors including the Mellor Award (2nd prize 1976; 1st prize 1977) and Boyer Award (1983) from MSKCC; Special Fellow (1976-1978) and Scholar Award (1978-1983) from the Leukemia Lymphoma Society; Merit Award, NCI (1987-1995); Karl Landsteiner Award, AABB (2002); E. Donnall Thomas Prize and Lecture, ASH (2007); Donald Metcalf Award, ISEH (2011); elected Fellow, AAAS (2012); Honorary Professor, Peking Union Medical College (2014); NHLBI Outstanding Investigator (R35) Award (2018-2025); and Lifetime Achievement Award, Cord Blood Association (Sept. 2019). He is past president of ISEH (1991) and ASH (2010).

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

I have worked on regulation of blood cell production (hematopoiesis) since my PhD thesis at NYU starting in the late 1960's, and with gene vectors for gene transduction to study regulation of hematopoietic stem (HSC) and progenitor (HPC) cells for over 25 years. My comments cover both areas, but with emphasis on cellular therapy. Progress made in both areas is nothing short of amazing. We can now rigorously phenotype HSCs and HPCs, have functional assays for them, and there are now different sources of HSCs and HPCs for transplantation. These were not available when I started. Use of cytokines (e.g. G-CSF) and small molecules (e.g. AMD3100=Plerixafor) for mobilization of peripheral blood (mPB), and use of cord blood (CB) for transplantation were not available. There was purification of proteins, production of recombinant cytokines and chemokines, now numbering in the hundreds, many of which are used for therapeutic benefit. There was development of monoclonal antibodies and cell-analyzers and -sorters, and use of monoclonal antibodies for clinical advantage. There is the emerging field of precision medicine. Immune therapy is an exciting area, but still much needs to be learned. There are a variety of viral and non-viral vectors, some which show promise for the emerging field of gene and immune cell therapy. Most of us did not envision such amazing advances in the late 1960's early 1970's. Then, research was descriptive. It is now heavily mechanistic. Few, if any, investigators believed in negative-regulators; there are now numerous negatively acting regulators. It was originally felt that if "regulatory" molecules didn't have well-defined specificity, they couldn't possibly have physiological relevance. We now know that most "regulators" have multiple functions. I anticipate the fields moving "light-years" ahead in future efforts to improve health care.

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

With the speed that scientific and clinical advances are being made in the cell and gene therapy fields, the following predictions are possibilities. We should have a better mechanistic understanding of cell-cell and cytokine-cell interactions, and how oxygen levels and the in-vivo microenvironment regulate functioning of HSCs and HPCs, and have an in depth insight into immunological cell interactions and their control for enhanced treatment of malignant and non-malignant diseases. CB transplantation will be vastly improved, with newer methods for collection of increased numbers of CB HSCs and HPCs, improvement in ex-vivo HSC/HPC expansion procedures, and enhancement of HSC homing. These will increase use of CB cells for clinical efficacy. There will be improvements in efficiency of collecting mobilized peripheral blood (mPB) from hard to mobilize donors. We will have better understanding of regenerative medicine possibilities. This field is still in its infancy for treatment potential. We will know if CB or other sources of cells can or cannot have positive therapeutic effects in non-hematopoietic transplants. There will be improvement in understanding and use of immune therapies and increases in gene therapy for a variety of disorders – with increased knowledge of gene transduction and best target cells for these vectors.

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

I have been involved in these fields of research for up to 49 years, and have never lost my interest or enthusiasm, even when work in the laboratory was at a low point. I never lose track of possibilities to bring what we learn in the laboratory to clinical testing by clinical investigators. Over the years, some clinical trials were initiated based on our laboratory findings. This includes AMD3100/Plerixafor to mobilize HSCs and HPCs, and to synergize with G-CSF and our studies on CB HSCs and HPCs which initiated the field of CB Hematopoietic Cell Transplantation. We continue to try and nurture this field through our laboratory studies. It is a joy to work in this area, and to interact with and collaborate with so many outstanding scientific and clinical investigators. Not everything we do results in useful information, but when it does, it is priceless.

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

Developments are only limited by our visions, desire, and enthusiasm to pursue as yet untested or unknown experiments. We are limited by numbers of investigators working in these fields, funding to pursue these studies, and recruitment and mentoring of the next generation of bright, motivated and dedicated young investigators. It is especially difficult for new investigators to get funded. We need to do our part to find and mentor new investigators and provide them with time and resources to succeed. We must also collaborate with other investigators for maximal output.

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

Love the area you are working in and if not move on to another. Pursue your work with enthusiasm and dedication. Not everything you try will provide positive results. You may have more failures than successes. Even one success can sustain you for a long time. Be persistent, but open to the possibility that perhaps you are at a "dead end", and need to move on. Find the "right mentor" or "mentors" and solicit advice when needed. Find a productive mentor (publishes and has NIH or comparable peer-reviewed funding), who you can get along with. Although hard, do not take negative critiques on papers or grants personally. Rather, use them to improve. Solicit help from other lab members, and students and faculty outside your laboratory. Have a mentoring committee. No one person has all the answers.