In memory of Hal E. Broxmeyer, a pluripotent scientist, pioneer, and mentor

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With great sadness, we residing in China heard the news that Professor Hal E. Broxmeyer passed away on December 8, 2021, due to complications of thyroid cancer. He was 77. We regret that we could not say goodbye in person to Hal, as he was fondly called by his students and colleagues around the world. We wish to express publicly our heartfelt gratitude to Hal for his many seminal contributions to the scientific research and applications, and profound impact on the careers of younger scientists like us. We are sure that our feeling and gratitude are also shared by hundreds of youngsters who are fortunate to have interactions with Hal. He will continue to be a bright star in the sky, inspiring and guiding us for many years to come.

Hal is well known, even beyond scientific and medical circles, as a pioneer of using cord blood as an alternative source of hematopoietic stem and progenitor cells (HSPCs) for clinical transplantation. Trained as a PhD-level scientist, Hal and his lab members did tremendous amount of bench work for years to prove the presence of abundant and functional HSPCs in cord blood. In 1988, his lab collected and cryopreserved cord blood from a sibling sister of Matthew Farrow, then a five-year old boy with Fanconi anemia. With the help of Dr. Eliane Gluckman at the L'Hopital St. Louis in Paris, the first cord blood transplantation was successfully performed on Matthew, demonstrating that cord blood could be a reliable source of HSPCs in clinic.[1,2] After this pioneering achievement, Hal strived to further improve the clinical efficacy of cord blood HSPC transplantation, including his recent work by mitigating extra-physiologic oxygen shock/stress (EPHOSS) and by targeting homing or ex vivo expansion of hematopoietic stem cells.[3–7]

Hal had published 838 peer-reviewed scientific papers with an H-index of 127. These papers have received more than 73,001 citations (based on Google Scholar, as of December 20, 2021). As a caring and effective mentor, he had trained directly 21 pre-doctoral and 56 post-doctoral/clinical fellows, and indirectly hundreds more nationally and internationally. Hal had served as Past President of the International Society of Experimental Hematology (ISEH, 1991) and the American Society of Hematology (ASH, 2010), among many other leadership positions. He was the first director of the Walther Oncology Center and chair of Microbiology and Immunology Department, Program Leader of NCI-Designated Indiana University Simon Cancer Center Program on Hematopoiesis and Hematologic Malignancies. Through these efforts Hal had helped many researchers worldwide, of which many became highly productive and independent investigators, including dozens of us who are working in China now. It is no surprise that in a scientific meeting in China held on December 18, 2021, two prominent Chinese scientists independently added few slides before their presentations, to memorize Hal (which is not easy for a Chinese to pronounce correctly). One of them is Prof. Tao Cheng, the Director of Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences (CAMS) and of Peking Union Medical School (PUMC). I (LC) expressed my gratitude and shared my fond memory of Hal in my opening remark for the 9th Summit of Cord Blood and Transplantation in China.

I did not meet in person with Hal until July 1998 at an annual ISEH meeting in Tampa. The ISEH meeting organizer put a party in the Sea World for meeting attendees including me, Hal, and his trainees. One of his trainees (a Chinese guy but I forgot his name) gave a talk on chemokines which I knew little at the time. During the social gathering, this Chinese trainee and I ran into each other and talked on various topics during many rides we did together. He asked what was like for a scientist to work for a company (then I worked for Osiris Therapeutics, Inc). I honestly told him how I felt at time. I also asked if he had talked to his mentor Hal. He told me that Hal was fully supportive for what he would choose to do. This reminded of my own PhD adviser Thomas Kelly who had confidence on me and supported me to choose less traveled paths at various stages of careers. Later on, we ran into Hal, who friendly chatted with me and other meeting attendees.

When I joined Johns Hopkins Medical School in early 1999 as a member of newly formed Division of Hematopoiesis and Immunology, I started to have more direct interactions with Hal during the attendance of ISEH and ASH annual meetings. In

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Figure 1. Prof. Hal Broxmeyer and Linzhao Cheng in Tianjin International Forum on Stem Cells, November 1, 2014.

Johns Hopkins, I also became a neighbor of Prof. Saul Sharkis, who did PhD together with Hal and Don Orlic in a small hematopoiesis lab affiliated with New York University; all three late became giants in the hematopoiesis field. Saul once told me stories about Hal, including his love of weight-lifting.

The most substantial research collaboration I did with Hal was done in 2010. When my team published one of first papers in derivation of human induced pluripotent stem cells (iPSCs) from postnatal human blood cells, Hal contacted me to seek collaboration on using cryopreserved blood cells to derive human iPSCs. We achieved this objective in both his Indiana lab and my lab in Johns Hopkins University, using various frozen cord blood including several samples that his team carefully cryopreserved for 21 to 23 years. Hal was the first author for this paper published in *Blood*.[8]

Perhaps the closest exchange I had with Hal was when he came to China for International Forum on Stem Cells in 2014. This conference organized by Prof. Tao Cheng was held every other year in Tianjin, China since 2008. Hal accepted the invitation as one of the two keynote speakers and finally made this trip in November 2014 (Fig. 1). I still remembered his comment "for clinical translation, the process should be as simple as possible," when another PhD scientist asked him a tough question after his talk.

After this meeting, I also accompanied Hal visiting other institutions in Tianjin. During and after the meeting, I knew Hal much better as a pioneering scientist and also as a mentor who had a humble background. He told me that he favors "underdogs" in scientific arena. Hal also told me the story that he helped several China-born scientists, including Prof. Xin-Yuan Fu who became a professor in Hal's Dept. of Microbiology and Immunology in Indiana University after Dr. Fu's departure from Yale. Obviously, Hal would not only favor China-born scientists.

I (Bin Guo[2]) worked as a postdoctoral fellow in Hal's lab from March 2015 to November 2018 (Fig. 2). I didn't have any research experience on hematopoietic stem cells when I joined his lab, but Hal offered me a position without any hesitation. When I discussed my projects with him, he always said "Tell me exactly how you performed this experiment and I want to make sure you did it in a right way." He was very patient, and he cares everybody's projects in his lab. He told everyone in his lab, "You should always keep trying, 'cause in that way you won't lose

Figure 2. Xinxin Huang (from left), Bin Guo, and Scott Cooper (Hal's long-term assistant) during the 2016 annual meeting in San Diego, USA.

anything." I spent 4 months to test many different hypotheses and finally found two projects that I can further investigate continuously. He had a unique way to get along with us. One day he came into the lab and stopped by my seat, said to me "Bin, this seat is a magic seat, you should publish four papers in my lab." I stood and replied seriously, "Hal, I will try my best." Then he laughed and said "I am kidding. No pressure."

One of the things that Hal enjoyed the most was sitting in front of his microscope and counting CFU colonies on Petri dishes. He scored all the CFU experiments for everyone in his lab even after his surgery. Hal was a warrior of science, and a champ of weightlifting. He won the Master's Weightlifting National Championship in 1990 and 1994 in his age group and weight division.

Hal worked extremely hard even in his home office during the pandemic. We sometimes gave updates to each other by email. I received his last email on November 9, 2021. "*Sorry for the very short reply before. I mainly work from home. The lab work is progressing well. We have about 8 papers submitted or in review. The big one with Hari Nakshatri on breast and ovarian cancer stem cells in context of hypoxia finally got accepted in Sci. Adv. I believe that it will be highly cited. First the reviewers rejected it but they misunderstood the crucial experiments. Hari and I pointed this out to the Editor and he gave us a chance to revise with a huge number of additional experiments and data. It took months to do but with good results that greatly enhanced the paper. It does get overwhelming being a principal investigator and always searching for more grant money. Just try to take it one step at a time. The fact that you are producing new work is a good sign. I am always happy to give you advice and I do not expect co-authorship for this. Best wishes to you and your family. Hal.*"

Working with Hal is one of the luckiest things in our life. We will deeply miss Hal, our beloved mentor and friend, in addition to be a world-class scientist and pioneer.

I (Xinxin Huang[3]) joined Hal's lab at 2012 and I continually felt super lucky to have Hal as my mentor for seven years. Hal was especially willing to help junior scientists, I still remember the first day we met at his office, we talked about current challenges within the hematology field, and in the end, he said "we are here to help you have a successful career." I was really grateful and greatly inspired. When discussing scientific questions, Hal was extremely serious and careful. He always offered constructive feedback, encouraged me to be motivated, and helped me initiate an independent career. I now have developed my own team at Fudan University, when I encounter difficulties during work, I often ask myself "what would Hal do?" Beyond science, Hal was good humored and interested in reading, classical music, and weightlifting. Once I drove him and two lab members to attend 14th Midwest Blood Club meeting in Memphis, Hal shared with us and played his collection of music from his cell phone in the car. When we arrived, we together visited Graceland, the home of Elvis Presley, who is the King of Rock and Roll. Hal was very excited to check out Elvis's photos, music, and memorabilia around the house. I have countless memories, precious memories with him. I clearly remember when Hal pointed to my head and made an unlock gesture, saying "Unlock you mind, this is what makes the real difference." I will remember his words and his legacy in the field forever.

May he rest in peace.

I (Tao Cheng) have known Hal for almost 25 years since I worked in David Scadden's laboratory. Because we have had overlapped interests in several research topics such as cell cycle control in hematopoietic cells, chemotaxis of hematopoietic cells, and applications of single cell gene analysis in hematopoietic studies, we communicated a few times every year when I was in the States. We met at ASH almost every year, sometime at ISEH. After I returned to China, I invited him to the IFSC meeting in early November of 2014, as mentioned by Linzhao above, and his visit was so great then. During his trip to Tianjin, he visited Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences (Fig. 3), where the first autologous hematopoietic stem cell transplantation (HSCT) in China was

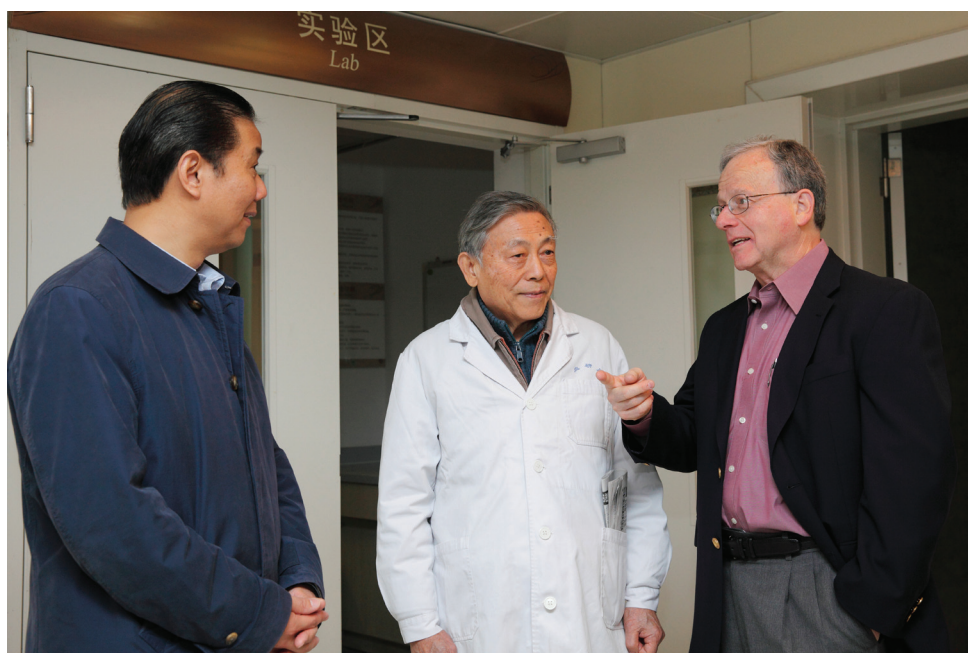

Figure 3. Hal Broxmeyer (right) and Kefu Wu (middle), the former director of State Key Laboratory of Experimental Hematology (SKLEH) and Tao Cheng (left), current director of SKLEH in the lab, 2014.

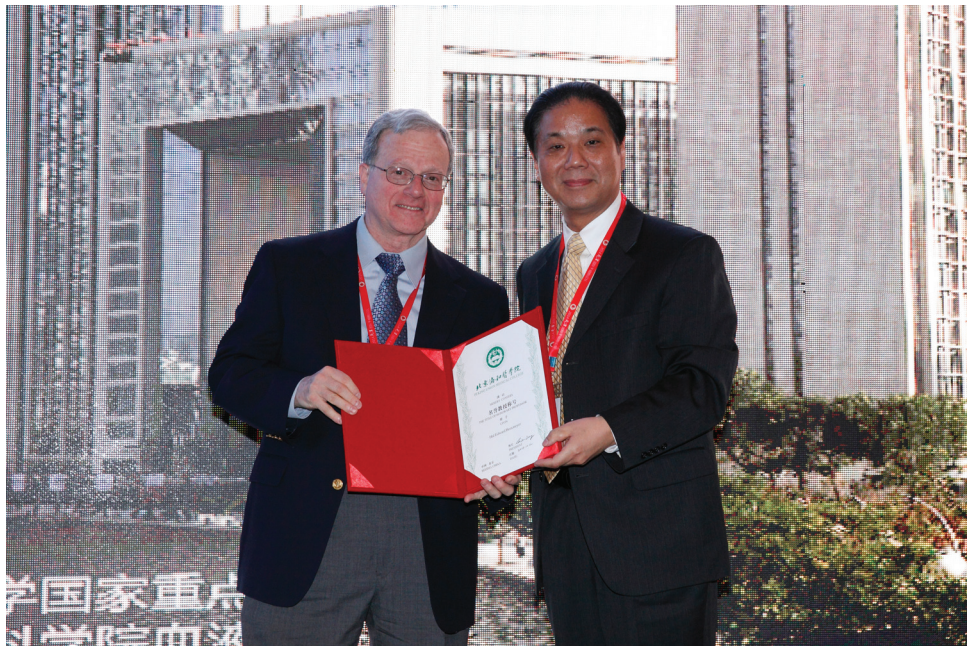

Figure 4. Hal was invited to be an honorary professor of Peking Union Medical College, China.

performed. In addition, to our great pleasure, he accepted the invitation to be an honorary professor of Peking Union Medical College (Fig. 4). However, I was surprised when I saw him at ASH in December of 2014, because he had developed thyroid cancer and then got a surgery. He presented his 15-minute talk with little voice due to the surgical procedure, which was hard for him.

In addition to what Linzhao and Bin describe above, I am quite impressed by his life-long energetic activities in research. He began his research career in 1970s and constantly conducted experimental work with high productivity. Even in 2021, he still published first authored papers, including his commentary for our bystander article in *Blood*.[9] He was a great mentor, and had trained many outstanding scientists from many countries in his laboratory. He was also very supportive to junior faculty. I had requested several times to him for recommendation letters and he was always happy to do so in a timely manner. He was a fast reviewer and never submitted his reviews late. He was also a great colleague who devoted substantial time for public service. He had served many NIH study sections.

In the preparation of *Blood Science*, Hal was extremely supportive. Soon after agreeing to join the editorial board, he contributed the 1st manuscript to *Blood Science* in a few weeks.[10] Every time he served as reviewer for the journal, he was always rigorous and critical, which tremendously helped to polish the manuscripts and guided the new investigators in their research.

In short, Hal was a prominent researcher in hematology and beyond, a great educator for his trainees, a strong supporter for career development of junior faculty, a synergistic collaborator between basic science and clinical medicine and a great colleague for public service. Knowing Hal or working with him is one of the luckiest things in our life. He was a true role model for us. We will deeply miss Hal.

REFERENCES

[1] Gluckman E, Broxmeyer HE, Auerbach AD, et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med* 1989;321(17):1174–1178.

[2] Broxmeyer HE, Douglas GW, Hangoc G, et al. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. *Proc Natl Acad Sci U S A* 1989;86(10):3828–3832.

[3] Christopherson KW2nd, Hangoc G, Mantel CR, Broxmeyer HE. Modulation of hematopoietic stem cell homing and engraftment by CD26. *Science* 2004;305(5686):1000–1003.

[4] Broxmeyer HE, Hoggatt J, O'Leary HA, et al. Dipeptidylpeptidase 4 negatively regulates colony-stimulating factor activity and stress hematopoiesis. *Nat Med* 2012;18(12):1786–1796.

[5] Mantel CR, O'Leary HA, Chitteti BR, et al. Enhancing hematopoietic stem cell transplantation efficacy by mitigating oxygen shock. *Cell* 2015;161(7):1553–1565.

[6] Guo B, Huang X, Cooper S, Broxmeyer HE. Glucocorticoid hormone-induced chromatin remodeling enhances human hematopoietic stem cell homing and engraftment. *Nat Med* 2017;23(4):424–428.

[7] Guo B, Huang X, Lee MR, Lee SA, Broxmeyer HE. Antagonism of PPAR-gamma signaling expands human hematopoietic stem and progenitor cells by enhancing glycolysis. *Nat Med* 2018;24(3):360–367.

[8] Broxmeyer HE, Lee M-R, Hangoc G, et al. Hematopoietic stem/progenitor cells, generation of induced pluripotent stem cells, and isolation of endothelial progenitors from 21- to 23.5-year cryopreserved cord blood. *Blood* 2011;117(18):4773–4777.

[9] Broxmeyer HE. Associated guilt: radiation/bystanders. *Blood* 2021;137(24):3314–3316.

[10] Broxmeyer HE. Quickly attainable and highly engrafting hematopoietic stem cells. *Blood Science* 2019;1(1):113–115.