

Legends and Legacies Book Chapters

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Dihua Yu, M.D., Ph.D.



**Professor of Molecular and Cellular Oncology
Nylene Eckles Distinguished Professorship
in Breast Cancer Research**

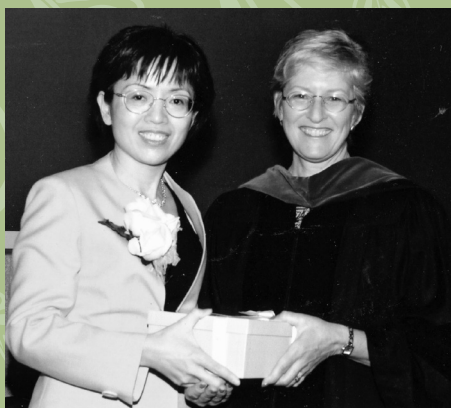


北京四週 1960.

Dihua was 15 months old when this photo was taken with her mother, Renping Yang.



Sizzling temperatures were part of Dihua's introduction to Houston and her Ph.D. training at The University of Texas Graduate School of Biomedical Sciences in 1986.



Dihua received the E. N. Cobb Faculty Scholar Award from Margaret Krijcke, Ph.D., at M. D. Anderson's Faculty Honors Convocation in 2000.



I was born into a physicians' family. Both of my parents are medical doctors. My father is the fifth generation of doctors in the Yu family, and my grandfather on my mother's side was the Chief Physician for General Zhang Xue-Liang in the 1930s. Not surprisingly, my parents expected me to be a physician. When I was in elementary school, my father told me that he and the previous generations of Yu family physicians had all published books, recording their specialties and experiences in dealing with very challenging patient cases. He told me that he expected to see my book when I grew up. I am glad that I did not disappoint him, and I recently gave him a new book that I had edited.

My mother was my role model as a career woman. She devoted herself to her patients and her family. She gave all her time, energy and resources to others and left almost nothing for herself. She was the chair of the Department of Internal Medicine at a more than 3,000-employee hospital in Beijing and frequently had to take care of over 80 patients a day in the clinic. Meanwhile, she managed to do almost everything for her three children (without much help from my father) so that we could concentrate on our studies. I still cannot figure out how she did it. She began teaching me three Chinese characters every day when I was 3 years of age; this equipped me with a middle-school-level reading ability when I entered the first grade. During my teenage years, my mother told me: "Dihua, external beauty can fade away as one gets old no matter how hard you try to keep it; on the other hand, the beauty inside a person — for example, a loving heart and a broad knowledge — can be kept and grows more as one ages and can be passed to future generations." Her wisdom has guided my life.

I was "a nerd" in school. I was given nicknames by other students for receiving perfect test scores (100 percent) in every subject. I loved to read all kinds of books. In addition to Chinese and foreign literature, history, philosophy and poems, I also enjoyed reading about Newton, Darwin, Copernicus, Galileo and Einstein. I was most fascinated and touched by the story of Madame Curie — I admired her and wanted to follow in her footsteps. I decided that I would not be the sixth generation of physicians in the Yu family and instead chose to study chemistry at Beijing University when I applied for college. However, my father believed that I would have a great future as a physician. He talked to the principal of my high school, who was a patient of his, and without consulting me, changed my college choice to study medicine at the Capital Medical University.

Thus, I unwillingly started my medical school training in 1978. Although I was a straight-A student in medical school, I did not enjoy the courses very much, as they mostly required memorizing descriptive, known facts. I was always more intrigued by novel scientific findings and was eager to know the unknown. However, I began to appreciate my medical education

after I started my internship in a hospital in Beijing. When we were making morning rounds, the patients would eagerly look at us to assess their diseases and trusted us with their lives. I started to understand why my parents loved their profession and why they were so dedicated to their patients. It was rewarding that I was able to help some patients. But there were also cases in which I felt helpless and powerless. I remember one instance of a young woman of my age who had colon cancer with liver metastasis and died right in front of me even with intensive care. We tried every treatment available in the 1980s but were unable to save her life. I was sad and disappointed that we physicians had such limited tools to deal with aggressive diseases.

This and several other similar incidents made me feel that medicine as an academic discipline was quite primitive and relied mostly on descriptive and correlative knowledge. I thought that we needed a better understanding of diseases and more effective medicines based on that understanding. This motivated me to go back to graduate school. Since I had developed an interest in understanding how the brain functions in human diseases, I entered an M.S. program in 1983, right after graduation from medical school, to study neuro-cardiophysiology (there was no Ph.D. program in China at that time). My mentor was Professor Zengfu Liu, from whom I learned not only how to address scientific questions related to a specific research project but also some general principles of conducting research. However, the research environment in China at that time was not favorable, and I frequently became very frustrated due to the lack of key reagents and needed equipment and to the difficulty of obtaining the most recent publications. Fortunately, after Richard Nixon's visit to China in the 1970s, the Chinese government initiated in the 1980s an "open door" policy that brought unprecedented changes. It became possible for us to study abroad and to learn from the best in an outstanding environment.

I came to the United States in the summer of 1986 and began my Ph.D. training at the Graduate School of Biomedical Sciences (GSBS) at The University of Texas Health Science Center in Houston. I first joined a protein chemistry lab in the UT Medical School for my thesis study. My mentor asked me to learn molecular cloning through tutorials under two newly recruited faculty, outstanding molecular biologists from Stanford University (Dr. David Loose) and MIT (Dr. Mien-Chie Hung). After 20 months of very challenging learning and hard work, I successfully cloned the full-length cDNA for a calmodulin-binding protein. However, my mentor then asked me to pass the cDNA clone to a postdoctoral fellow in the lab for functional study and assigned me to clone another gene. This meant that I had to start my thesis research all over again as a third-year graduate student! I share this experience because things like this can happen to anyone, and, when they do, you just need to find a way to move on. I expressed my

frustration to the GSBS student advisor, Ms. Gaughan. Fortunately, the GSBS has a good tradition of protecting students, and I was advised to move to a different lab for my thesis study.

In October 1988, I joined Dr. Mien-Chie Hung's laboratory at M. D. Anderson Cancer Center for my Ph.D. thesis research. Mien-Chie is one of the hardest-working scientists I know, and his love of research is contagious! He always challenged us to ask important questions and to think outside the current dogma. I was inspired by him to clone the tumor growth factor-beta receptor so that we could study its function in human cancer, and to study transcriptional regulation of the HER2/ErbB2/neu oncogene so that we could identify a new approach to turn off the oncogene. I truly enjoyed learning state-of-the-art molecular biology techniques and making new discoveries. Interestingly, my research project studying the regulation and function of the HER2/ErbB2 oncogene provided me with opportunities not only to learn the fundamental approaches of basic science but also to link basic research back to medicine. Specifically, my thesis research revealed that the adenovirus E1A gene transcriptionally represses the HER2/neu gene and inhibits HER2/neu-induced transformation, tumorigenesis, and metastasis. Based on my findings and on additional research by other trainees along the same lines, M. D. Anderson and several other institutions performed clinical trials using E1A to treat HER2-positive cancer patients and demonstrated some clinical efficacy. This gave me a rewarding feeling, similar to what I had experienced while I was doing my internship. It also made me realize that by asking clinically important questions, I as a scientist also could have the opportunity to help many patients, as my parents had always wanted me to do.

Another important part of my thesis research was to study the oncogenic function of HER2/neu. Since the first patient whose death I had witnessed died of cancer metastasis and since M. D. Anderson has an outstanding environment for studying cancer metastasis, I initiated an investigation of whether HER2/neu promotes cancer metastasis using a defined experimental system rather than a correlative study. I clearly demonstrated that overexpression of HER2/neu induced higher metastatic potential in cancer cells. Back in the early 1990s, metastasis research was done mostly at the general biology or cell biology level. I, on the other hand, was able to apply molecular approaches for understanding mechanisms of cancer metastasis because of my molecular biology training from Mien-Chie and the cancer biology expertise at M. D. Anderson. This provided me with a unique opportunity when Dr. Suresh Mohla at the National Cancer Institute (NCI) initiated an R03 grant mechanism to solicit proposals using molecular biology approaches to study cancer metastasis. I submitted an R03 proposal with my medical degree while I was still a GSBS student.

In April 1991, I was informed that my R03 application had received a top score and would be one of the 10 proposals nationwide to be funded by R03 grants. Before I was notified about the R03 grant in early 1991, I had also applied for a postdoctoral position in the lab of Dr. Bert Vogelstein, who had been named by the journal *Science* as scientist of the year in 1990. At about the same time I received the grant notice, I also got a handwritten letter from Dr. Vogelstein telling me that he had an opening for my postdoctoral training in his laboratory in the summer of 1991. My career was at a crossroads! I was debating whether to stay at M. D. Anderson to carry out the research in the funded R03 grant or to move to Johns Hopkins for postdoctoral training with Dr. Vogelstein. I had several discussions with Mien-Chie and with Dr. Garth Nicolson, who was the chair of the Department of Tumor Biology at that time. Garth said that he could not understand why I was even considering giving up the incoming grant to be a postdoctoral fellow. He then promised to promote me to instructor right away and to assign me a lab space if I stayed at M. D. Anderson, but I was still having difficulty making my decision.

Then, I found that I was pregnant with my first child, and that coming event convinced me to stay at M. D. Anderson, as I was sure I could succeed in carrying out the research proposed in the R03 grant in this nurturing and friendly environment even while pregnant. I was awarded the R03 NIH grant in July 1991, three months after I graduated from the Ph.D. program. That year, the NIH funding rate was at a historically low point and it was very difficult to obtain grants, even for established investigators. My success in obtaining the R03 was partially due to my exposure to grant writing while I was a graduate student, as I had always worked with Mien-Chie when he was submitting his grant applications. I share this experience with students and postdoctoral fellows to let them know that assisting your mentor can better equip you for future career challenges. In September 1991, I was given the junior faculty title of instructor and was assigned two benches at M. D. Anderson. I will never know whether I made the best decision.

Pursuing the R03 grant allowed me to publish four first-authored papers, but it also generated more scientific questions. Therefore, I decided to apply for an R29 grant in 1992. As I was actively writing the grant application, I had a chance to meet an invited speaker, who was a distinguished senior scientist. When he heard that I was writing an R29 proposal, he told me, "My advice is don't waste your time. Reviewers are not going to give a five-year NIH grant to an instructor, especially in the current funding environment." As you can imagine, this was a very discouraging message. But, I told myself, "My chance is zero if I do not apply, but my opportunity will be greater than zero if I do apply." So I made substantial efforts to prepare the R29 proposal, and the application was reviewed by the Path B

Study Section. To this day, I am very grateful that the reviewers of that study section gave me outstanding and constructive suggestions. I revised one cycle and received the funding notification in 1993.

After this, I started to look for a tenure-track assistant professorship to obtain an opportunity for an independent research career. At that time, the Department of Tumor Biology at M. D. Anderson had such an opening, so I applied for it. After a couple of months, Garth Nicolson, the department chair, told me that he had had a faculty meeting to discuss my application and that most of the faculty had supported it but one had said “I don’t think she is ready.” Garth told me that it would be very difficult to have a smooth start to such a challenging career with an opponent in the same department. He said, however, that there were many other opportunities at the institution: for example, Dr. Raphael Pollock in the Department of Surgical Oncology was recruiting for a tenure-track assistant professor. Garth told me that if I were interested, he would be happy to pass my CV on.

Within a few days, Raphael contacted me about the available position in Surgical Oncology, and we had a very nice conversation. He told me that he had received more than 80 CVs for the position and was most impressed by mine, especially by my grant funding. He wanted to offer me the position and bring it to upper-level leaders for approval. However, I had something else in my mind. I told him that because a colleague at the institution thought that I was not ready for a tenure-track assistant professorship, I needed to prove my credentials to my colleagues *and* to myself. Thus, I did not want to accept his offer right away but first wanted to seriously look for a tenure-track assistant professor position outside the institution. I would only take the M. D. Anderson offer after I had a written offer from outside. I am thankful that Raphael was so understanding and supportive. He agreed to my proposal and said he would hold the position for me. I sent application letters to 12 universities/institutes for tenure-track assistant professor positions and was invited for an interview by seven. After I had received three offers, I declined the other invitations. I then brought the written offers back to Raphael and asked him to put them into my file. I told him that in the future, should anyone question my qualifications for a tenure-track position at M. D. Anderson, he could show them these written offers.

Raphael and I began scientific collaborations in January 1994. I ran my breast cancer research lab and, in addition, Raphael asked me to help build a sarcoma research lab with him. My parents had always told me that, by strengthening my boss’s position, I was strengthening my own position as well. I therefore put my heart and soul into leading those two research groups. I provided daily guidance to students, postdoctoral fellows and research assistants in both labs. We published many high-quality papers and received multiple NIH and Department of Defense (DOD) grants. Several

faculty inquired how I could successfully manage to run two labs that had different research focuses while many faculty were stressed by running one lab with one general research direction. They asked, “What is your secret?” But there was no secret! I worked about 100 hours a week and did not take a single day of vacation in 13 years. Although I have now moved to the Department of Molecular and Cellular Oncology, I am positive that those 13 years of hard work allowed me to build a solid scientific base and taught me leadership. My career rapidly advanced from junior faculty to my current established status because of the quick accumulation of knowledge, experience, leadership skills, and success in research, education and service to the scientific community that were the direct result of working very hard. Just as my Mom had told me when I was a teenager, the skills and knowledge within me had accumulated and grown. Working closely with Raphael, I also learned some of his techniques for handling sensitive issues. In some cases, these were eye-opening experiences that allowed me to gain some measure of political wisdom.

I also have been very fortunate to have Mien-Chie as my mentor even after I began my independent research career. Mien-Chie and I have regular meetings and discussions. He sets very high standards in research, education and services. These have been my career challenges. Whenever colleagues and friends told me “You work too hard,” I smiled and told them that I knew another person who worked even harder, and I meant Mien-Chie. Inspired by him, I tell myself “We only have this life once, so we should do something important with it.” Because of my medical background, I identified translational research as my focus. I want to use research approaches to answer and address clinically important questions. For example, our studies on the mechanisms of Herceptin resistance revealed that loss of PTEN rendered breast cancers resistant to Herceptin. We then developed combination therapy strategies that allow us to overcome Herceptin resistance mediated by PTEN loss. This has led to a phase I/II clinical trial, and it has been really rewarding to see that about half the patients on the trial have benefited from this newly developed strategy. Our work has also been recognized by the scientific community: in a commentary in *Nature News*, in the *New England Journal of Medicine*, and in a 2006 *Science* article by the previous NIH director, Dr. Harold Varmus, reviewing 50 years of progress in developing anticancer therapies.

As far as my personal life, I guess the younger generation would consider my current lifestyle “boring.” I was an amateur dancer in elementary and middle school (and occasionally in medical school and graduate school in China). In high school and beyond in China, I spent my weekends visiting art galleries, attending concerts or going to theatre shows. I got married when I was a graduate student in China. My husband, Ping, majored in electrical

engineering as an undergraduate and in graduate school at Rice University. He supports me and takes a major share of our family responsibilities. As mentioned previously, I was pregnant with my first child in 1991, when I was the principal investigator on the funded R03 grant. I did not take a single day off during pregnancy and I did not stop bench work. I returned to work in blue jeans 12 days after my son was born, and I attended a local scientific meeting. At the meeting, I won first prize for a poster presentation, an award that provided me with full travel support to an international meeting in Singapore.

In 1998, when I was in the eighth month of pregnancy with my daughter, my lab and Raphael's lab were scheduled to move from the Yellow Zone to the newly built Tan Zone lab space. As the lab head, I organized all elements of the move for the two labs without taking any of Raphael's time. After one week of intensive moving, we pretty much settled into our new location. Before I went home that evening, I took a final tour of the new lab and was relieved that the move had gone smoothly. However, when I returned to my office, suddenly my water broke. Since I was only eight months pregnant, I had not yet arranged for transportation to the hospital. My husband was an hour's drive away from M. D. Anderson, and I did not want to risk having the baby in my office, so I walked quietly and slowly to Garage 5 to drive myself to the Woman's Hospital of Texas. Fortunately, in the garage I met Mien-Chie, who was on his way to dinner with several faculty friends. Seeing my situation, he postponed the dinner and dropped me at the hospital building entrance. I took an elevator upstairs to the delivery room and had my daughter at 1:30 a.m. on August 8, 1988. At 10 a.m. that day, I called the lab to tell them that my daughter had been born early and that I wouldn't be able to make the 10:30 a.m. meeting that I had originally scheduled to discuss revision of a manuscript for *Molecular Cell*. I came back to work two weeks later, led the team effort to finalize the revision, and submitted the revised manuscript before the deadline. The paper was accepted for publication soon afterward.

I have to say that it is not easy to juggle personal and professional demands, but I am fortunate to have a supportive family. Three days before I delivered my son, my mother flew from Beijing to Houston to help me. She had just had a mastectomy after being diagnosed with node-positive breast cancer. Although she could not even lift her left arm then, she insisted on taking care of my son so that I could sleep through the night and go work the next day fully energized. Later, her breast cancer progressed with lung metastases and she had a second surgery. A few years later, she had bone and brain metastasis. While she was hospitalized in Beijing, I had a few opportunities to speak at scientific meetings in China and got to visit her. I could tell from her eyes that she was very happy to see me. However, she

would always say, “You should go back. I don’t want you to slow down your work for me.” My mother had a big loving heart and was totally selfless. After she left Houston, my in-laws came here. They have given their love and care to my children, allowing me to better concentrate on my work. Meanwhile, I did find a way to be with my children while working. I began to bring my son to work with me on weekends when he was 2 years old. We would bring computer games or fun toys, and, while he played, I would talk with colleagues and lab members. Then, we would go to the cafeteria and have a baked potato, one of my son’s favorite foods. Amazingly, coming to work with Mom on weekends became a real treat for him. After he entered middle school, I began bringing my daughter to work on some weekends, and she also very much enjoys this routine. Although I sometimes feel guilty for not spending enough time with my children, they seem to understand and are both good students who hold high academic standards themselves. Some people ask what I do during my free time. I do not have much free time, but I do find time to read. Reading gives me peace of mind, enjoyment and keeps me young at heart. I also go to the gym to run on the treadmill on Saturdays and Sundays. At this stage of my career, I also have many opportunities to travel around the world, which not only meets my professional needs but also enriches my personal experience.

Although biomedical research is challenging and demanding, it can be really rewarding. I feel that I have one of the best jobs in the world. I once told my children that I wouldn’t trade jobs with President Bush, and I meant it. My profession allows me to learn new things and make new discoveries every day. Our research brings new diagnostic tools and novel therapeutics to benefit patients. As an educator, I have the unique pleasure of bringing up a younger generation of scientists. I have a typical “Chinese Mom” mentality in that I have a high expectation for my trainees and care about them as if they were my children. When my trainees show progress in their studies and receive awards, I am as happy and proud as when I get straight-A report cards and award plaques from my children. I enjoy doing research and also cherish my ability to provide younger scientists with needed help. I am fortunate that my dream of following Madame Curie’s path in research has partially come true. My research and education efforts are having an impact on patients’ lives and on young peoples’ careers, and this gives me a rewarding sense of achievement that cannot be measured by money or fame. Whenever I meet young people who demonstrate a true love of research, I naturally want to pass along my knowledge and experience to help them succeed. For those young people who share my dream, I have a few special, specific pieces of advice. First, it is important to have a clear vision and a clear career goal and to persistently work toward it without distractions. I have had some trainees who were very bright

with great potential but who were easily distracted and did not use their time wisely. Second, as a scientist and researcher, one needs to be resilient and remain optimistic. Experimentation can frequently fail and requires searching for the correct answers/approaches again and again. I have seen trainees get depressed when their experiments do not work and then stop pursuing the solutions. Unfortunately, this will never lead one out of a bad cycle. Handling failure with a positive mindset leads to final success, which will be even more rewarding. Third, find a good mentor who can guide you and inspire you to develop a successful biomedical research career. I am very fortunate to have Dr. Mien-Chie Hung as my mentor. More recently, Dr. Margaret Kripke has given me critical career advice and shared her wisdom on leadership with me. She encouraged me to participate in the Faculty Leadership Academy, where I learned to take a balanced approach when handling conflict rather than the avoidance or compromise approaches I was used to taking. As a high-achieving woman scientist and a senior woman faculty leader, Dr. Kripke is an important role model for me.

Currently, I have two important professional missions. First, I want to perform high-quality cancer research that will impact patient care. Second, I want to provide leadership and serve as an active educator to bring up the younger generation of scientists so that they will be ready to continue the fight against cancer and succeed in their careers. I enjoy working with my colleagues and trainees who share my vision and passion in fulfilling these missions. The daily opportunity to interact with bright people who have enthusiastic minds is a precious gift. Life is good.



Epilogue

Soon after joining The University of Texas M. D. Anderson Cancer Center as Provost and Executive Vice President, I was delighted to discover that the institution had launched a formal effort focused on the recruitment, retention and development of women faculty. Elizabeth Travis, Ph.D., who prior to my arrival was appointed by Margaret Kripke, Ph.D., leads the new Office of Women Faculty Programs, which is dedicated to the advancement of women faculty and the establishment of M. D. Anderson as an international leader in offering exciting opportunities for women physicians and scientists.

Much of M. D. Anderson's recent progress in cancer research, patient care, education and prevention has been possible because of Margaret's contributions over more than two decades. Not only has she blazed a trail for other women to follow, but she also has inspired substantial improvements to help all faculty. For example, she influenced the creation of an academic leadership academy for faculty training, she instituted a rigorous laboratory review process for each of our laboratory investigators and she established periodic external reviews of all basic science departments. In addition to serving as the first female faculty member selected for top management at M. D. Anderson, she has worked tirelessly during two terms on the three-member President's Cancer Panel to advance national strategies to control cancer.

The Office of Women Faculty Programs is especially meaningful to me because I have strongly supported development of women's careers in academic medicine and understand very well the impact of this initiative. I came to M. D. Anderson from the Vanderbilt-Ingram Cancer Center in Tennessee, an institution where about half of the basic science department chairs are women and where the leadership team is fairly balanced in its gender mix. That diversity, which served Vanderbilt well, certainly is a key component for the continuing success of M. D. Anderson. I am extremely proud that Jennifer Pietenpol, Ph.D., who served as my research director, has recently been named Director of the Vanderbilt-Ingram Cancer Center. Supporting and advancing the careers of women faculty is a vital issue at all academic medical institutions, where women still tend to remain under-represented on the faculty and more heavily concentrated at entry level ranks. A few years ago, Eric Neilson, M.D., Chairman of Medicine at Vanderbilt University Medical School, published a collection of stories about women faculty at Vanderbilt, and it was very well received. When Liz Travis told me about plans to develop a similar book at M. D. Anderson, I enthusiastically encouraged her efforts.