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Life Has Ups and Downs, but Always Ask Questions

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"You should always ask questions, the bigger the better. If you ask big questions, you get big answers."

Francis Crick

This essay was begun on Christmas Day, 2013, in Vienna, Austria. My nephew had just lost his job, and a good friend's son was having personal troubles. Both young men told me how hard their lives were, especially in comparison with mine. I was moved to write out my own experiences with life's difficulties to share with them. I have now updated this essay in July 2022.

Life's events resemble the fractal patterns of temperature: up and down, never smooth. There are always ups and downs. But one should always ask good questions, even at the most difficult times. Good questions can sometimes be life-changing.

My own life follows such a pattern. In Chinese wisdom, it is the story of *The White Horse* (*Sai Weng lost his horse*)*.

LIFE IS ABOUT RECOGNIZING AND TAKING OPPORTUNITIES

Life is about recognizing opportunities, and sometimes taking risks, big and small, and making decisive decisions, sometimes quickly and sometimes slowly and carefully, sometimes correctly and sometimes incorrectly, and facing the consequences. Many good opportunities come and go. If we do not recognize and seize them immediately, life would be totally different.

Sometimes it is a single-minded pursuit, and sometimes it is a chance encounter or a serendipitous discovery that alters the course of a person's life. One must have a prepared mind to recognize such an opportunity or make such a discovery. One sometimes wonders, "what if the opportunity was not taken?" Commenting on the discovery of the DNA double helix structure, Francis Crick remarked: "*It's true that by blundering about we stumbled on gold, but the fact remains that we were looking for gold.*"

EARLY DAYS (1957–1960)

In 1957, when I was 4 years old, Mao Zedong launched the Hundred Flowers Campaign and the Great Leap Forward Campaign. Mao encouraged everyone to speak out and to make sincere suggestions to improve the communist rule. But Mao soon realized there were many people who opposed his tyrannical rule, and he soon harshly purged those who criticized him and his policies.

One of the vice presidents in my father's workplace made good and reasonable suggestions to improve the communist party's relationship with ordinary people. He was soon demoted, labeled a rightist and purged from his job. At the time, my father, Zhang Zen Ming (his name means "honest person"), worked in the human resources unit. He was asked to write the demotion document for the vice president. After he gathered the evidence and materials, conducted interviews, he wrote a report stating that the vice president did not say anything wrong; that he simply made some honest suggestions. As a consequence, my father, then 35, was also soon demoted, labeled a rightist, and purged from his job. He was sent away to a labor and re-education camp. When my mother, my brother, and I moved from Chongqing to Chengdu (in those days, 400 kilometers meant about an 8-hour train ride), my father did not come with us (Figure 1d).

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Figure 1. **My formative years.** *a) In 1958, at the age of 5. b) My father, Zhang Zenming, and my sister Zhang Xuejun (now a medical doctor). My mother was sent away to the May 7 Re-education Labor Camp during the China Cultural Revolution. c) In 1970, with teenage friends, we all grew up together in Chengdu. d) Around 1958 in Chengdu, with my mother Zhao Xindi and my brother Zhang Hongguang. My father was left behind in a Chongqing labor camp to punish him for speaking the truth in 1957. e) With friends Qu Qiang, Fu Chenming and Gao Qiang just before leaving for Chinese army in December 1970. f) With Liu Chuguang at Sichuan University in 1977.*

My father finally rejoined us in the summer of 1959, but my mother was soon sent away to reform the countryside in another county about 500 kilometers away. The party leaders deliberately separated my parents. To re-educate him, my father was allowed to work in the canteen for the school. It was considered the lowest job. Gradually because of his good behavior, he was promoted to a manager of the canteen. After Deng Xiaoping came to be the Chinese president in 1978, he started reforming the communist party and openly apologized to those who had been called rightists. My father was finally vindicated and rehabilitated in 1982. In 1984, he retired. His entire working life was ruined from being honest and speaking out. However, for over 25 years, he never said a word about what happened to him. I only learned it from him 2 years after I had moved to the United States.

ELEMENTARY SCHOOL (1960–1966)

I went to elementary school in Chengdu from 1960 to 1966. I walked around 2 kilometers each way to go to school. In the early 1960s, elementary schools underwent reforms to change the teaching of complex Chinese characters to that of simplified ones so it would be easier for young students and illiterate people to learn to read and write. Thus, I had to learn the same characters twice. As a result, I can recognize and read most of the complex Chinese characters, but I am unable to write them. Also, in the early 1960s, several new elementary schools were opened to accommodate the increasing baby boomer population. So, in the middle of the semester, our class was transferred to another elementary school and had to repeat second grade. Even in elementary school, I was very inquisitive and always asked a lot of questions. I was a very curious and diligent student. I studied hard, and did well in my studies. Thus, I received a very solid elementary-school education for 6 years. This turned out to be extremely important later.

TEENAGE YEARS IN CHENGDU (1966–1970)

The onset of the Cultural Revolution in June 1966 resulted in complete chaos across China. Red guards traveled freely

around China destroying the traditional cultural and historic buildings. I was caught up in the fervor and wanted to join the Red Guards too, but I was too young. Also in 1966, all schools were closed for 3 years. Most books, especially science books, were burned or destroyed since China didn't invent modern science. When the middle school finally reopened in the fall of 1969, I entered the 7th grade at Chengdu 7th Middle School. But I only stayed for about 2 months. Most of the studies involved politics. There was very little mathematics and science, and I learned nothing useful. In October 1969, I was sent to my father's home village on the other side of the country, to treat a health problem. My father was originally from a poor village, Nanhou Village #2 in Rizhao County, south of Qingdao, in Shandong Province. It is about 1,500 kilometers distant from Chengdu. I lived with my father's family for almost a year. I had no academic studies at all. During that time, I learned a lot of farm labor work. I learned to fetch and carry water daily, including during the cold, icy winter. I learned to harvest yam and peanuts, and to cook local food. It was the most physical labor I had done in my life. In late summer 1970, I returned to Chengdu to continue middle school for about 3 months. Then in December 1970, when I was 17, I had the opportunity to join the Chinese army as a solider. Joining the army promised better opportunities and regular pay, not to mention regular meals. At the time, it was quite a privilege to be accepted in the army. So ended my primary and secondary schooling. Altogether, I missed 3 years of middle school and all of high school.

IN THE CHINESE ARMY IN SICHUAN PROVINCE (1971–1975)

Initially, it was exciting to be a solider, as I was away from my parents and spent day and night with young men of similar age. I was assigned to be a messenger to carry documents and orders between military units. In that position I had the opportunity to be around top officers.

Since my childhood, I have always been very inquisitive and always asked a lot of questions of many subjects. In the military, however, orders must be obeyed, not questioned, but old habits die hard, and I soon got into very serious trouble. I asked a lot of questions when I was with the top military officers. They could not, or were afraid to, answer my questions. I was transferred out of the communication unit, to keep me away from the top officers. I was first demoted to feeding horses. But I still had opportunity to ask questions to top officers since the horses are for them to ride, so my troubles continued. Soon, I was further demoted to feeding pigs, so I no longer had opportunity to ask questions to the top officers. Finally, I ended up as a cook in the canteen feeding soldiers, a fate roughly similar to my father's, around 15 years earlier. My father was extremely alarmed and concerned about my two demotions because it reminded him of his own demotion in 1957.

Fortunately, as a cook, I had a lot of time to read and write since I did not have to participate in political studies, which were always a waste of time. The only available books were Karl Marx, Friedrich Engels, Lenin, and Mao. I read a lot of them. I particularly enjoyed Engels since his writings about science were more refreshing and accessible than others. After reading the works and carefully thinking, I wrote a lengthy letter (without keeping a copy) to the highest Chinese military central command, complaining that soldiers were poorly trained since they spent most of their time sitting around studying political articles. I pointed out that if the soldiers do not get enough training, there will be heavy casualties if a war breaks out. Unfortunately, this turned out to be exactly the case during the China–Vietnam border conflict in 1979.

WORK IN CHENGDU PIG HAIR FACTORY, CHINA (1975–1977)

After I left the army in January 1975, I returned to Chengdu and lived with my parents again. During that time, there were few jobs, and I was fully aware that I could not compete against the princelings of government officials to land one. Therefore, I took a job in a factory cleaning pig hair for export. I reasoned that since I had served in the army, I might eventually have a chance to do something else when other opportunities arose. But it was a huge gamble. I had no idea how long it would take for such opportunities to arise. In the meantime, I worked very hard in the dusty and terribly smelly pig hair factory. This experience also made its mark on me. Even today, I find it very difficult to tolerate dust and dirt.

I was friendly and got along well with most of the other factory workers. I learned about their lives which were very different from mine. We played basketball and other games together. In those days, China had 6 working days per week. The 8-hour days, 6 days a week, were routine, repetitive, and very boring. There seemed to be no opportunities for advancement. But I was very hungry for scientific knowledge. I bought "Young People's Self Study Guide" books for mathematics, physics, chemistry, and English to slowly and painfully learn something on my own in the evenings and on Sundays. I tried to make up for missing so many years of school. From this experience I learned the value of good study habits.

Finally, some universities began to re-open. There were discussions concerning whether someone from the pig hair factory should go to Sichuan University to learn how to extract some useful proteins from the pig hairs since pig hair is made of proteins. Several people in the pig hair factory had finished high school and had already collaborated with some professors to learn the extraction methods, so they were the

obvious candidates to go to the university. However, in the 1970s one's family background mattered a great deal. Despite their qualified educational background, they were not selected. Instead, I was recommended by the workers and selected because of my military service, and because I was well-liked by most workers. I was to enter Sichuan University without an entrance exam in September 1976 as a member of the class of "Students of Workers, Farmers and Soldiers."

Then, Mao Zedong died on September 9, 1976. Everything in China froze, including universities. It was not clear when or if the universities would re-open. Thinking back, it is hard to believe that Mao's death had such a huge negative impact on China. This is because the decisions were made by a very few top leaders without real concerns for the people or the devastating negative impact. Finally, universities reopened in January 1977. All accepted students had to wait 4 months to enter universities.

STUDY AT SICHUAN UNIVERSITY (1977–1980)

My father was very much against the idea of university. He had never been to university himself, and he was very worried that I would get into trouble with too many questions. He forbade me to attend. We had numerous heated arguments. It was a terrible dilemma. At the time, I did not know what my father had been through himself in 1957. However, my mother had graduated from Fudan University, and she strongly supported me. It took a long time, but she finally convinced my father that I should go. She understood the opportunity may not come again.

At the ripe old age of 24, I finally entered Sichuan University. Today, by the age of 24, most students have already finished their bachelor's or even master's degrees, and some may even be 2–3 years into their doctoral studies. Initially I had great difficulty grasping many subjects, especially mathematics, physics, chemistry, and English since I essentially lacked a basic middle- and high-school education despite my diligent self-studies. I failed most tests and examinations. My academic performance was almost at the bottom of my class of 30 students. I was completely devastated, since I had been a top student in elementary school.

Undeterred, I struggled very hard to take several middle- and high-school courses on my own while at the same time taking calculus and differential equations. I had lost many years of schooling and I knew I had to work very hard to catch up. Despite my poor grades, I continuously asked a lot of questions to most teachers on many subjects. A very kind organic chemistry professor, Ma Zhanxiong, observed my struggles and was very sympathetic. He volunteered to tutor me in chemistry and we met frequently. Professor Ma recognized my perseverance for overcoming difficulties. He invited me to his home on campus to meet his wife and sons, and we became very good friends. My parents were also very appreciative to Professor Ma for his kindness to me. I kept in touch with Professor Ma even after I came to MIT and visited him and his family several times whenever I was back in Chengdu. He was very proud of what I have become.

During China's Cultural Revolution, most science textbooks were either banned or burned outright. For all 3 years of our studies at Sichuan University, we did not have a single textbook. All we had were copies of the teachers' lecture notes. Some of them were from the 1960s and had very little current information. Scientific journals were rare. We never saw or even heard of *Nature*, *Science*, *Cell*, *JACS*, *PNAS*, or *Scientific American*. Fortunately, some eager, diligent, and resourceful teachers had learned about some of the latest developments in science, including the discovery of the structure of the DNA double helix.

At Sichuan University, I was exposed to many new subjects and new information. I learned about DNA and RNA and other biological molecules. I learned that DNA is always right-handed. One day I asked my professor, "*Can DNA ever be left-handed*?" My professor did not know the answer. Not long after that, a *Science News* article came out. It had the December 1979 *Nature* cover article by Alexander Rich's laboratory, reporting their discovery of a DNA molecule with a left-handed helix structure that he called Z-DNA. I was delighted and fascinated. I wanted to learn more about this Z-DNA structure. I dreamed of studying with Alexander Rich. Little did I know that one day my dream would really come true.

After 3 years of constant struggles, I had gradually improved my grades but I never reached the top 25% of my class. I was never an A level student in Sichuan University. However, many teachers remembered me because I asked them all kinds of questions, frequently and repeatedly. Asking good questions makes a very big impression on others (see Box 1).

AN UNUSUAL LETTER FROM THE UNITED STATES

It is worth mentioning that from 1949, the newly communist People's Republic of China completely closed itself off from the West. The United States was considered an especially evil and imperialistic enemy. So it was world-changing that in 1971, Henry Kissinger began making secret visits to China. He was laying the groundwork for Richard Nixon's historical China visit in February 1972. They were opening up the possibility of re-establishing a diplomatic relationship between the United States and China. After several years of preparation, in 1979, Jimmy Carter formally normalized the diplomatic relationship. This opening had a good side-effect. Letters could be exchanged between ordinary people in the two countries for the first time in 30 years.

One day I learned from my brother that our father had received a letter from the United States. I pressed my father to show it to me. Finally in mid-1979, my father reluctantly showed me the one-page letter from his aunt Chen Xiuting and her son Shouri Chang (Chang is spelled as Zhang in China). They were living in Portland, Oregon. I had never heard of these relatives before. This was not surprising, because under Mao's rule such a relationship would immediately put one's family in political danger with the very real possibility of a job demotion or worse. My father later told me that his aunt moved to Korea in the 1920s and they lost contact for over 40 years. She and her husband, my father's uncle Zhang Chuanyu visited my grandfather Zhang Chuanhe's family in 1938 after the Japanese army invaded China and destroyed my grandfather's house. They generously provided money to rebuild the house. (How Zhang Chuanyu and Chen Xiuting met, married and escaped to South Korea, that eventually led me to come to the United States, is a fascinating story in itself, one that needs another essay.)

APPLYING FOR A CHINESE PASSPORT (1979–1980)

After letter exchanges, Chen Xiuting learned that I was a student in university. She immediately invited me to study in the United States, specifically at Portland State University in Oregon. But first, I needed a Chinese passport. In the 1970s, perhaps one in a few million Chinese citizens had a passport. Most never even saw one. China was still almost completely closed to the outside world. Thus, when I tried to apply for a passport, no one knew where to start. After resourceful and persistent efforts, I eventually found my way from Sichuan University to the Chengdu Police Station to the Sichuan Security Department, all the way to the Central Ministry of Security in Beijing. Along the way there were many rejections amid endless documentation and inquiries into my parents, my background, interviews, and more. After more than a year, in mid-1980 I became the first person from Sichuan Province, then home to more than 100 million people, ever to receive a private passport.

ARRIVAL IN PORTLAND, OREGON (1980)

After obtaining my passport, I obtained a US F-1 student visa without much difficulty because so few Chinese applied for US visas in 1980. I exchanged the equivalent of my 1 month's salary for $20.00, the maximum allowance exchange then. Thus, with US$20 in my pocket, I arrived in Portland, Oregon.

In the late 1970s, the Chinese propaganda machine had informed the population that the Beijing airport was the best in the world because eight airplanes could board passengers all at the same time. Since China was closed to the outside world for 30 years, we believed this. We were all totally brainwashed. Imagine my astonishment when I first landed at Narita Airport in Japan and then Sea-Tac airport near Seattle where hundreds of planes were boarding passengers simultaneously. The big lie bubble was burst instantly. That taught me to think about other propaganda machines and other big lies.

In the United States, I had to quickly learn English, to listen, read, speak, and write. At Sichuan University, I had learned some English, but most of what I was taught was essentially political nonsense. Little was useful and I had hardly any opportunity to hear and to speak English. When I was asked by the US custom officer what things I had in my suitcase, I wanted to tell him "arts," but he heard "ox" and was astonished. I could read and write, albeit with a lot of mistakes, but I could hardly understand anything and I could not speak very much at all. To gain a better understanding of English, I watched children's educational TV programs such as Sesame Street. These provided me with an English education too. At the time I wished I could understand even 50% of what was on TV.

STUDY AT PORTLAND STATE UNIVERSITY, OREGON (SEPTEMBER 1980–AUGUST 1982)

At first, I was only permitted to take English as a Second Language classes at Portland State University. I could read and write poor English, but I could hardly understand the lectures in the classroom. Through diligent study and hard work, my English gradually improved and I started to audit other courses without formally registering. I did passably well for courses that did not require much English, such as organic chemistry, physical chemistry, and parts of biochemistry. I received Bs and As as an auditing student. But I did very poorly for physiology and the parts of biochemistry that required a lot of English. I struggled very hard to try to understand the mid-term exam questions, but I could not understand half of them, thus I did very poorly. I received mostly Cs and even a D for these classes. However, because I always asked a lot of questions, professors remembered and tried to help me despite my poor grades. Luckily, I did better for the final and received a B– for biochemistry. So again, I was never an A level student at Portland State University.

I also worked in my uncle's and aunt's Chinese restaurant from 4:00 p.m. to 11:00 p.m. on Fridays and Saturdays to earn money to pay for tuition. Because my English was very poor, I first cleaned tables and washed dishes. When my English gradually improved, I took orders and served the tables. I sometimes made ordering mistakes and my uncle was not very happy about it. The restaurant was always very busy since the food was quite good and inexpensive. Even in my father's village, I had never worked as hard physically as I did at the restaurant. I collapsed twice due to total physical exhaustion since I was the only person serving about 15 tables.

But it was a good place to practice English. To broaden my English and to learn American culture, I asked customers a lot of questions about their interests and learned from them, and in return, they gave me very good tips.

I also volunteered to do research in different labs during the week in the afternoons, evenings, and on weekends as well as in the summer breaks. Here I learned how to do scientific research, first in a biophysics laboratory and later in two different microbiology laboratories. I asked the professors in these laboratories a lot of questions. They all realized that I was a curious and capable student.

My poor English also had other serious consequences. In April 1982 after completing about 1.5 years of studies including many required chemistry graduate courses, I asked the Head of Admissions and, later, the head of the Chemistry Department when I would receive my master's degree. To my utter surprise, they looked at my record and told me that I was not even enrolled in the master's program! I was stunned and speechless.

They suggested that I apply to other universities since the application deadline had already passed for admission to the autumn 1982 master's degree program at Portland State University. As a result, I immediately gathered the information to apply to graduate school at several University of California campuses, including Davis, Riverside and Santa Barbara. I studied to take the Graduate Record Examination (GRE). It was extremely difficult to prepare for the GRE, especially the English part; I had never seen many of the unusual English words in the GRE preparation book. I spent a lot of time preparing for it, but in the end, my score for the English part was only 7%. Random guesses could have earned me a much better score.

I soon received two formal rejection letters. UC Davis simply stated that the application deadline had already passed. UC Riverside said that my 3-year Sichuan University B.S. degree was not equivalent to a UC Riverside B.S. Disappointed but undeterred, I immediately prepared to apply for undergraduate studies, looking into UC Santa Cruz and UC Los Angeles.

One of the biochemistry professors did not see my research capability and only saw my poor grades, even though I asked her many questions in my broken English about her lectures and about content in the textbooks. In her mind I was not a good student. I asked her if she would write me a letter of recommendation for graduate school. She not only refused, but also told me directly "You are not good enough to be a graduate student. In fact, no one would even hire you to wash lab dishes." I was disappointed, but was not down completely, since I perhaps did not completely understand or believe what she was really saying. That lack of understanding saved my spirit.

However, the microbiology professor Jack Myers and biophysics professor Kwan Hsu suggested that I apply to the graduate schools of UC Berkeley (where they both earned their Ph.D.s) and UCLA because they closely observed my research capability and were at the receiving end of my endless scientific questions for more than a year. They both wrote very strong recommendation letters for my application that ultimately led to my acceptance as a graduate student at UC Santa Barbara. I was totally and pleasantly surprised, and of course delighted. It was a dream came true since UC Santa Barbara was my first choice!

When I later told the biochemistry professor that I was accepted by UC Santa Barbara as a master's student, she was completely astounded since UC Santa Barbara is a much higher-ranking research university than Portland State University. Also, I knew my acceptance was certainly not due to my GRE English score, and perhaps not even my academic transcripts since I did not have a very good GPA. What got me accepted into UC Santa Barbara? Several strong recommendation letters from the professors with whom I did research. This UC Santa Barbara graduate school acceptance was a turning point and changed my life for better and forever. I sometimes wonder what would have happened if I had not been accepted by UC Santa Barbara. I would certainly have had a totally different experience and a different life.

STUDY AT UC SANTA BARBARA (SEPTEMBER 1982–JUNE 1988)

Although my English had improved after 2 years of intense and diligent study, I was still far from understanding English adequately. I often made mistakes. I misunderstood others and others misunderstood me. UC Santa Barbara also had the quarter system, 11 weeks per quarter, and I always struggled with the quarter system. I believe the quarter system is too rushed, which is good for lecturers but not at all good for students to truly master knowledge.

I remember in particular how difficult my six-unit microbiology class was. I could not remember the Latin names of numerous microorganisms. It did not help that the professor also lectured in a soft voice that I barely heard, let alone understood. Thus, I did very poorly for two midterms and the final examination despite the fact that I went regularly to the teaching assistant's office hours to get help. I received a C for the final grade. The only thing that saved me was the lab experiment part of the class. Because I asked a lot of questions to the graduate student TAs for the microbiology class, they knew that I understood more than answering the exam questions.

In the end, though, I learned a lot more than my poor grade suggested. That C immediately placed me below the required graduate student GPA 3.0 of a B or better. Luckily, I received an A– and a B for two other courses and three seminar classes. But my overall GPA was still below the required

3.0 for my first quarter at UCSB; not a very good start. So, I was placed under observation for further consideration. If I continued with a GPA below 3.0, I would be asked to leave graduate school. My academic standing was in serious danger. For the winter quarter, I only took three regular classes and three seminar classes totaling 12 units. Unfortunately, I had to withdraw from a class since I did not do well for the two midterms, although I constantly asked the professor questions and learned a great deal. Thus, I only had nine units for the winter quarter, three units short for a full-time student. This, too, was a very serious threat for my academic standing.

In the fall of 1982, I worked very hard for my three one-unit literature seminar classes: Seminar in Nucleic Acids, Seminar in Eukaryotic Genetics, and Seminar in Virology. I spent countless hours preparing for each of the presentations. I not only read the original papers thoroughly and carefully, but I also read many background papers and historical papers (that was before the internet era and I had to read these papers in the library). The professors who taught the classes were impressed. One of them, genetics Professor Eduardo Orias who heard me to give two presentations in two separate seminar classes, asked me to join his lab at the end of the autumn quarter in 1982. I was totally surprised, flattered, and immediately agreed. Later another professor of virology also asked me to join his lab after he heard my two presentations. This was again a life-changing experience.

When I anxiously told Professor Orias that I did not do very well in my microbiology class and had a GPA below 3.0, he looked at me and said "*grades only measure one's ability to understand particular knowledge at a particular time*." Professor Orias was very wise, and I have never forgotten his wisdom and advice. Further, he saved me from being asked to leave graduate school. I now routinely tell my students Orias's wisdom. It also suggests that thoroughly understanding the original research is more important than having a general knowledge of a subject or a good grade.

AN UNEXPECTED SETBACK (1987)

In September 1987, my 3-year-old son was diagnosed with childhood acute lymphoblast leukemia (ALL). It was the most devastating and shocking news in my life. We were completely unprepared. My son had 68% cancer cells with double chromosome translocations in his bone marrow. The oncology doctors refused to provide any prognosis. The greatest irony was that a few months earlier, I had submitted a fellowship proposal to the American Cancer Society to study chromosome translocations in leukemia cells. Thus, I had a very good understanding of what the treatment entailed. My son was treated very intensively and aggressively, first at the Children's Hospital in Los Angeles, about 200 kilometers from Santa Barbara.

He was later treated continuously for 3 years through the Jimmy Fund at the Dana-Farber Cancer Institute in Boston from June 1988 to June 1991. He had access to the latest cocktail chemotherapy drugs of that era. It was a terrible time. He experienced numerous serious side effects. Miraculously, his leukemia was completely cured and is now fine and healthy. He has had a normal life, going to public schools in Cambridge and Lexington, Massachusetts and graduating from university in 2007.

RESEARCH AND TEACHING AT MASSACHUSETTS INSTITUTE OF TECHNOLOGY (JUNE 1988–PRESENT)

In early 1988, I was awarded a fellowship from the American Cancer Society to study chromosome translocations in leukemia cells in the laboratory of Professor Alexander Rich at MIT. Professor Rich had proposed that a segment of left-handed DNA, called Z-DNA, could influence genetic recombination. At the molecular level, chromosome translocation is a DNA recombination event. I had been very interested in Rich's lab since I was an undergraduate student in China in 1979, when Rich and colleagues reported the discovery of left-handed DNA in *Nature* (it was the cover story). In early 1979, I had asked my biochemistry professor at Sichuan University if there were left-handed helices since we were told that most molecular helices, namely, alpha-helix in proteins, the DNA double helix, and helices in cellulose all seemed to be right-handed. It was a simple scientific question. No one had observed left-handed molecular helices in nature. So, the discovery of the left-handed DNA double helix excited me a great deal. I decided then and there that I was determined to eventually work in Alexander Rich's laboratory. It was a big dream, and completely unrealistic from where I stood in 1979. However, 9 years later, my dream came true. I had to go through many detours, but I arrived in the Rich Lab at MIT on June 27, 1988.

It was the most rewarding experience of my life. The lab was home to over 30 energetic, driven, and intelligent students and postdocs from many countries around the world. It was a thrilling experience. Plus, Alex's lab was fertile ground for ideas. I thrived there and enjoyed it immensely. I made many lifelong close friends in the Rich Lab, including Martin Egli, Stefan Wölfl, Reinhard Gessner, Burghardt Wittig, Mischa Dorbic, Brian Johnston, Ned Seeman, Sung-Hou Kim, Joel Sussman, Andy Wang, and Alexander Rich himself and his family. Alex also introduced me to his close friends, some of the founders of molecular biology. They included Francis Crick, Leslie Orgel, Max Perutz, Sidney Brenner, Carleton Gajdusek, John Edsall, Jack Dunitz, Har Gobind Khorana, Jean-Marie Lehn, Ada Yonath, Frank Westheimer, Jack Strominger, Alexander Varshavsky, Ephraim Katzir, and Meir Wilchek (Figures 2 to 6).

But even there, not everything went smoothly. I soon found out that I could not obtain the leukemia cells required

Figure 2. **Photos from my personal collection.** *a) Alexander Rich (left) and Francis Crick (right) with DNA models in Alex's MIT office, 1988. I asked Alex to stand next to the left-handed Z-DNA and Francis to stand next to the right-handed B-DNA models for their discoveries of left-handed and right-handed DNA structures, respectively. b) with Francis Crick and Alexander Rich in the Rich Lab, 1988. Alex brought many leading scientists to the lab to meet his students and postdocs. c) With my Ph.D. advisor Dr. Eduardo Orias in the lab during my visit to my alma mater University of California at Santa Barbara in 2005. I have kept in continuous contact with Dr. Orias. d) I visited Francis Crick at the Salk Institute on August 26, 1991 and took this photo. During another visit in 1994 I asked Francis Crick to sign the photo. I kept in contact with Francis and Odile Crick for many years and visited them several times in their home in La Jolla, California.*

for my proposed fellowship research since the NIH had just closed down the MIT tissue culture center. As a result, I had to quickly switch to another system. Baker's yeast was the first choice since it can be grown in the lab in large quantities inexpensively. Also, there were many labs, including Alex Varshavsky and Lenny Guarente working on yeast at MIT then, so there were ample tools, methods, protocols, and knowledge.

Yeast is also an excellent system to study recombination. After I started the project, I learned that there was a previous postdoc in the Rich Lab who had tried to purify the left-handed Z-DNA-binding protein from yeast and failed. Undeterred, or perhaps foolhardy, I decided to try again using a better assay system. After I developed method of a methylated CG-polymer DNA band shift assay, I made numerous attempts and failed. But I persisted and eventually purified a protein from yeast in late 1989, which I named Zuotin (Zuo means left in Chinese) for its ability to bind the left-handed DNA. In 1990, I also cloned and hand-sequenced the Zuotin gene (ZUO1). I had a lot of difficulty sequencing part of the DNA and failed repeatedly. I persisted and searched for alternative ways. After diluting the sequencing nucleotides 10- to 20-fold (a highly unorthodox strategy), I finally sequenced through the difficult region. I found the region had a lot of repeats with high CG content. To my surprise, after translating the DNA sequence into protein, this region has also the protein sequence repeats, somewhat like the repeating musical notes in a melody[1].

After I obtained the ZUO1 gene, I tried to sub-clone it into an expression vector in order to produce large amounts of proteins. But by accident, I picked the wrong plasmid vector since the plasmid box was full of small vials of DNA plasmids with very small hand-written labels. It took me over 3 months to do various experiments as I tried to figure out why there was no expression; why I could not obtain any results. Very frustrated, I finally sequenced the plasmid vector, and found to my great dismay that the DNA sequence was not the plasmid I thought it was. It was my own mistake; I had no one to blame except myself. I now tell my students and postdocs to be extremely careful when cloning to use the right plasmid.

During careful inspection of the Zuotin protein sequence, I discovered a segment of repeating sequence,

Figure 3. **Photos from my personal collection.** *a) In 2013, with Alex Rich at his summer house in Woods Hole, Massachusetts. b) In 2013, with Alex Rich and Robert Langer at Woods Hole. c) 1993, with Alex Rich and his former postdocs Martin Egli and Charlotte Hauser at the Symposium Genome for the 40th anniversary of the DNA double helix in Paris, France. d) With George Klein of the Karolinska Institute in 1999. Earlier, Klein sent me his scientific papers on leukemia and EBV, relevant to my son's leukemia. e) With Carl-Ivar Brändén of the Karolinska Institute and David Eisenberg of University of California at Los Angeles at a small workshop on self-assembling peptides and proteins in Crete, Greece, 2003.*

n-AEAEAKAKAEAEAKAK-c[2]. This was the first discovery of a self-assembling peptide. I then made a detour and pursued it with my full energy (or irrational exuberance) for the next 14 years. It is quite thrilling. I started from sheer scientific curiosity about an unexpected discovery, to investigate the repeated sequence in Zuotin, which led me to almost fully understanding how self-assembly of peptides takes place at the molecular level. Our self-assembling peptide nanofiber scaffold material has been commercialized to great success. In 2001, I borrowed $50,000 from a violinist businessman and friend to found a startup company, 3DMatrix. Within 12 years, it had reached a valuation of over $1 billion[3]. All involved benefitted financially, including MIT (Figure 7a).

After the discovery, I remained at MIT, as a principal investigator first at the Center for Biomedical Engineering (CBE) for 15 years (1997–2012) until the CBE was officially closed in June 2012. I am now at the MIT Media Lab (Figure 8).

After I had an independent appointment in January 1997, I obtained substantial funding from the US government, foundations, companies, and private donors and my lab flourished with five postdocs, two visiting scientists and a few students. In 2001 Professor Joseph Jacobson of the Media Lab and I wrote a far-reaching grant proposal to DARPA for the electronic control of biological molecules. The grant was soon awarded. However, after the US military invaded Iraq in 2003, DARPA terminated the signed contract and withdrew the remaining funding. My lab funding collapsed.

In this emergency, I spoke with Alex Rich, who kindly and immediately injected $20,000 from his own discretionary account to my research account in order to keep my lab afloat. Luckily, an unexpected visitor came to my lab. The new business head of Olympus Corp in Japan became interested in my self-assembling peptide materials research. They not only quickly funded my lab, but also sent capable scientists to my lab as visiting scientists to learn about the materials. Thus, my lab was saved.

OLFACTORY RECEPTORS—MEMBRANE PROTEINS

In 2004, my interests turned away from self-assembling peptides and the materials they can make, to an entirely new problem. I wanted to study olfactory receptors—the molecules on cell membranes that receive odorant molecules and send their signals to the brain. Around this time, I accepted another unexpected visitor, the CTO of an electronic company ROHM in Japan. After some discussion, ROHM funded my

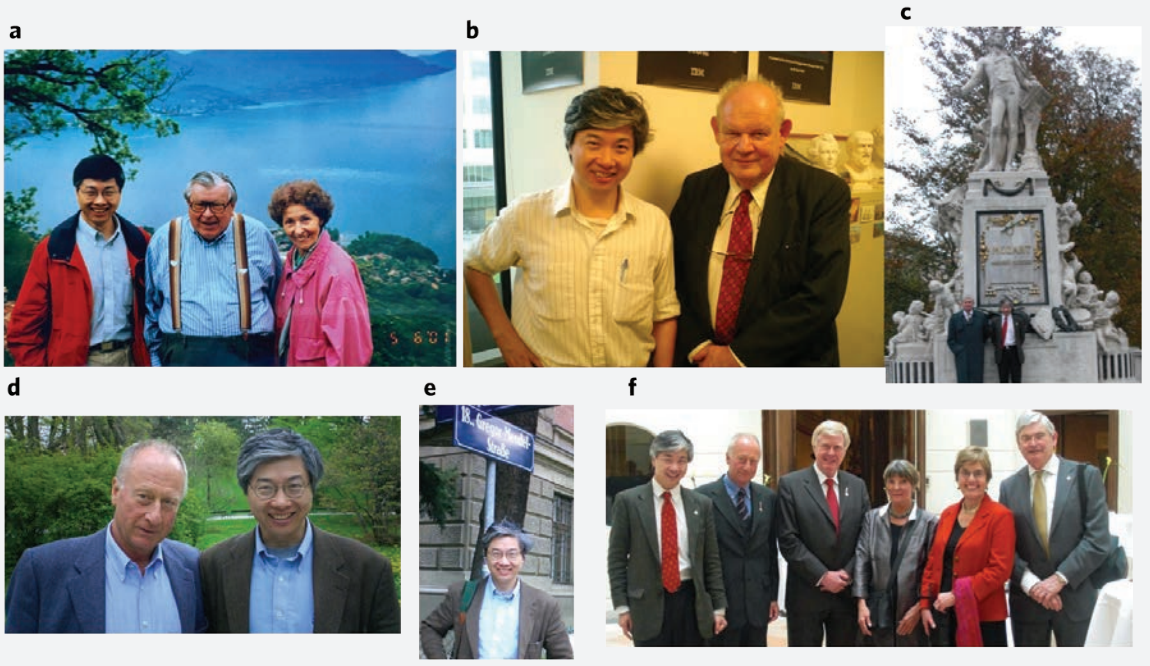

Figure 4. **Various photos from my collection.** *a) With Carleton Gajdusek and Gabriele Zu Rhein at Lago Maggiore, Italy in 2001. b) With the mathematician and father of Fractal Geometry, Benoit Mandelbrot in my MIT office in 2005. c) In 2009 with Sir Alan Fersht, University of Cambridge, UK, in front of the Wolfgang Amadeus Mozart Monument in Vienna, d) 2005 with Uwe Sleytr in Vienna, e) On the street named for Gregor Mendel, in Vienna, Austria, 2005. f) 2009, with Uwe Sleytr, Wolfgang Knoll, Henny Sleytr, Marilyn Fersht and Alan Fersht.*

newly initiated research on study of smell receptors, which is a member of the G protein-coupled receptor (GPCR) family. By 2005, my lab was again flourishing, full of excitement with new research activities with students, postdocs, and researchers from Sweden, the Netherlands, Greece, Italy, Switzerland, United Kingdom, Canada, United States, Japan, China, and Indonesia (Figure 8).

Since I wanted to change my research direction to work on the notoriously difficult membrane proteins, I needed to learn new knowledge. I applied for a John Simon Guggenheim Fellowship in 2005 and obtained the fellowship in April 2006. From September 2006 to March 2007, I took a 6-month academic sabbatical as a John Simon Guggenheim Fellow at the University of Cambridge, UK[4]. I was affiliated with laboratories in both Materials Science and Biochemistry and was invited as an honorary member of the room by Alan Fersht at Gonville and Caius College. I thoroughly enjoyed meeting many leading scientists there and became friends with them including Alan Fersht, Greg Winter, Tom Blundell, Chris Dobson, Alan Windle, Nick Gay, Nigel Unwin, and Richard Henderson.

However, more downs came in 2011 in early 2012.

In July 2009, I met a wealthy Chinese businessman in Shenzhen. This man served in the Chinese army at the same time I served. We were in the same big unit, but we never met. However, we knew many people in common. He became very interested in my MIT research, and decided to sponsor it. I thus went to Shenzhen many times during 2009–2011. In March 2010 he signed a research sponsor contract with MIT's Office of Sponsored Programs to support my research on biosolar energy for 4 years at US$400,000 per year. He also came to visit me in July 2010. However, he never paid the agreed funding and breached his contract. His breach of contract put me in a terrible situation. In 2011, after more than a year without any payments to MIT, the MIT Office of General Consul eventually sent a very strong-worded letter. His company relented and paid the penalty of >$200K to MIT.

My lab had started working on olfactory receptors in early 2004 since this is an unsolved and challenging question. We know a great deal about our genome, but we still do not understand how we smell. After a few years of working without a governmental grant, my lab was awarded a DARPA contract under the title Microfluidic Integrated Transduction Nose, namely, "MIT RealNose" in early 2008 (~$10M for 39 months) to pursue this line of research with the final goal of making a sensing device. With the significant funding, my lab expanded.

However, during phase I (~$4M for 18 months), the DARPA Program manager abruptly left DARPA to take a civilian job, thus the entire project was first put in jeopardy and later

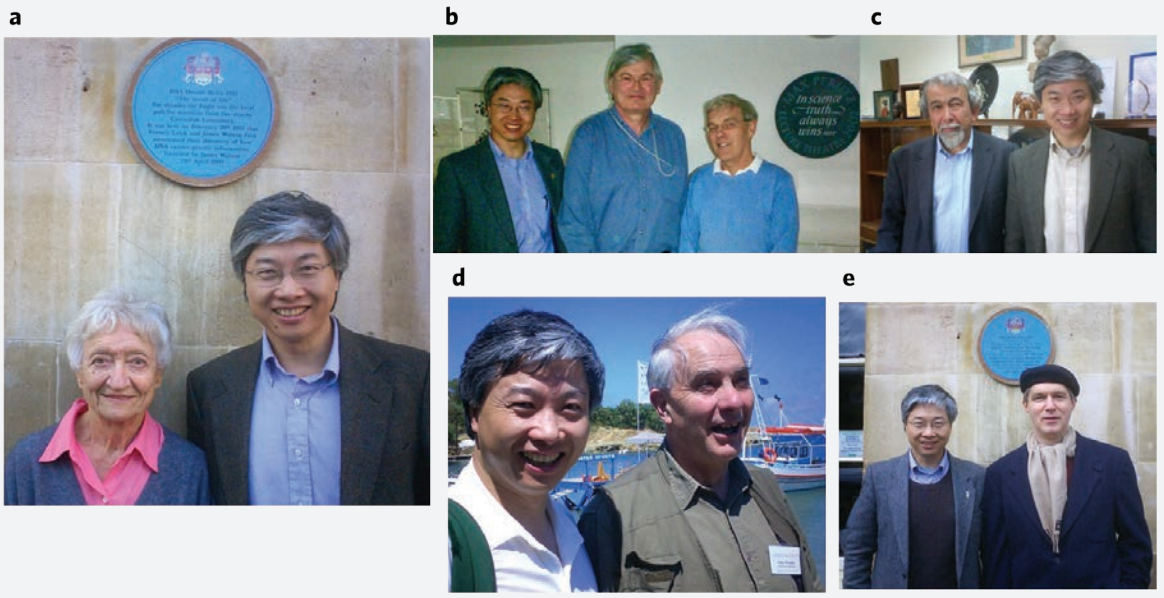

Figure 5. **Various photos from my collection.** *a) In 2006 with Odile Crick in front of the DNA Double Helix plaque on the wall of the Eagle's Pub. Odile Crick gave me a tour of the Colleges of the University of Cambridge, especially Gonville Caius College where Francis Crick was a Fellow. b) In 2006, with Alan Fersht and Richard Henderson at MRC-Laboratory of Molecular Biology, where Richard Henderson hosted me to give a scientific seminar. c) My host, Sir Tom Blundell, in whose lab I spent a considerable amount of time during sabbatical. d) With Alan Windle, in whose lab I also spent time while on sabbatical. e) With Martin Egli in 2007, in Cambridge, England.*

cancelled in March 2010. However, because this is very interesting work, another DARPA manager initiated another program, and we were able to continue part of the work in 2011. But one Co-PI (as a non-MIT contractor) in the program refused to pay MIT overhead. He got into a heated argument with the Director of MIT Office of Sponsored Program and MIT's Vice President for Research. The grant was in grave danger.

At the same time, my 5-year NIH grant (2005–2010) came to an end. With the breach of contract by the Chinese company, the end of NIH funding, the cancellation of my first DARPA contract and the second DARPA contract in doubt, my lab again had difficulty getting funding quickly.

In January 2011, in order to keep my lab afloat, I borrowed $400K. Fortunately, several researchers in my lab had their own funding. On October 23, 2011 after my startup 3DMatrix went IPO, I also put $100K into my MIT gift account (total personal money $500,000). In December 2011, I returned the borrowed money in cash or in 3DMatrix shares (the shares split twice).

During the funding crisis in April 2011, the Director of the CBE resigned because he could not obtain funding for the center either. I was soon told that CBE would be closed on June 30, 2012. And the head of Biological Engineering wrote me and asked me to find another lab space even though at that time he had no jurisdiction over the CBE lab space. I met with several leading scientists, including Alex Rich, Robert Langer, Susan Lindquist, and Joseph Jacobson, asking them help me find a suitable lab space. In June 2011, they wrote a strong supporting letter on my behalf to then Associate Provost for Space (later MIT Provost), and in July 2011 they met with the MIT Provost (later MIT President). The MIT Provost called a few deans to inquire about possible lab space, but no one was willing to share their precious lab space.

In the meantime, I repeatedly received demands from the head of the Department of Biological Engineering to move my lab out of its lab space in May 2012. The head wrote that the lab space must be renovated for new use. It was strange since the lab space was only opened in 2003, everything was standardized and nothing was damaged, and it was in excellent condition. My suspicion was later confirmed; a year after I moved out the lab, almost nothing was renovated!

The CBE was scheduled to be closed on June 30, 2012. But the department head gave me an ultimatum that I must move by Friday June 8, 2012. He refused to allow me even a delay to Monday June 11. I could not move on Friday

Figure 6. **Various photos of author's collection.** *a) With son Niklas in 1992, at MIT Killian Court. b) With Niklas in Woods Hole in 1994. c) With Carl-Ivar Brändén and Maria Masucci of the Karolinska Institute in 1999. I was there as an external Ph.D. thesis committee member of a student Dr. Zhao Bian. d) With Benoit Mandelbrot and Ingemar Ernberg of the Karolinska Institute in 2005. e) With Steve Yang in 2009, my former Ph.D. student in early 2000s. We visited the active volcano Krakatoa in Indonesia. f) With Horst Vogel and Bengt Nordén in 2005. g) Bengt Nordén with Andreas Mershin at the 2005 American Chemical Society meeting in San Diego. During the dinner, we discussed encouraging young people to study science, especially molecular science. It was the impetus to establishing Molecular Frontiers Foundation in 2006.*

June 8 due to MIT's commencement ceremonies. I had to move everything out on June 7, 2012. We were still doing experiments using the instruments on June 6! But under such great pressure, we had to temporarily moved the lab equipment into Alex Rich's lab in the Biology Department; then moved again 3 weeks later to the Media Lab. If I had moved on June 30, I would only have had to move once! This was a very unpleasant experience.

I am now in the MIT Media Lab. I have already had long-term collaborations with Professor Joseph Jacobson and Dr. Andreas Mershin. I obtained many joint grants with him and was on several Ph.D. students' thesis committees there. And I also teach a class there. I have been a MIT freshman advisor and running a seminar class for MIT freshmen since 1994. The MIT students, postdocs, and researchers are fearless, driven, work hard, take their own initiatives and are resourceful.

CONCEIVING THE QTY CODE

As noted above, I had started to study olfactory receptors. These entail understanding the membrane proteins that function in the olfactory neural pathway. Membrane proteins are partly hydrophilic (water soluble) and partly hydrophobic. This makes them notoriously difficult to study in the laboratory *in vitro*. I therefore needed a better method for studying membrane proteins. Membrane proteins are important, not only for olfactory receptors. Approximately 26% of the human genome codes for membrane proteins that are crucial for both internal and external cellular communications.

The need for a better method of studying membrane proteins led me to invent a simple and elegant molecular QTY code, namely glutamine (Q), Threonine (T), and Tyrosine (Y) to systematically replace the hydrophobic amino acids Leucine (L), Valine (V), Isoleucine (I), and Phenylalanine (F) in the seven transmembrane alpha-helices of G protein-coupled receptors (GPCRs)[5]. When we made GPCRs designed for water solubility using the QTY code, we found that despite changing 46%–56% of the transmembrane alpha-helices, water-soluble QTY variants still maintain stable structures, and biological function, namely, ligand-binding activities, in an aqueous environment. The implications are that the QTY code is likely a profoundly useful tool for designing

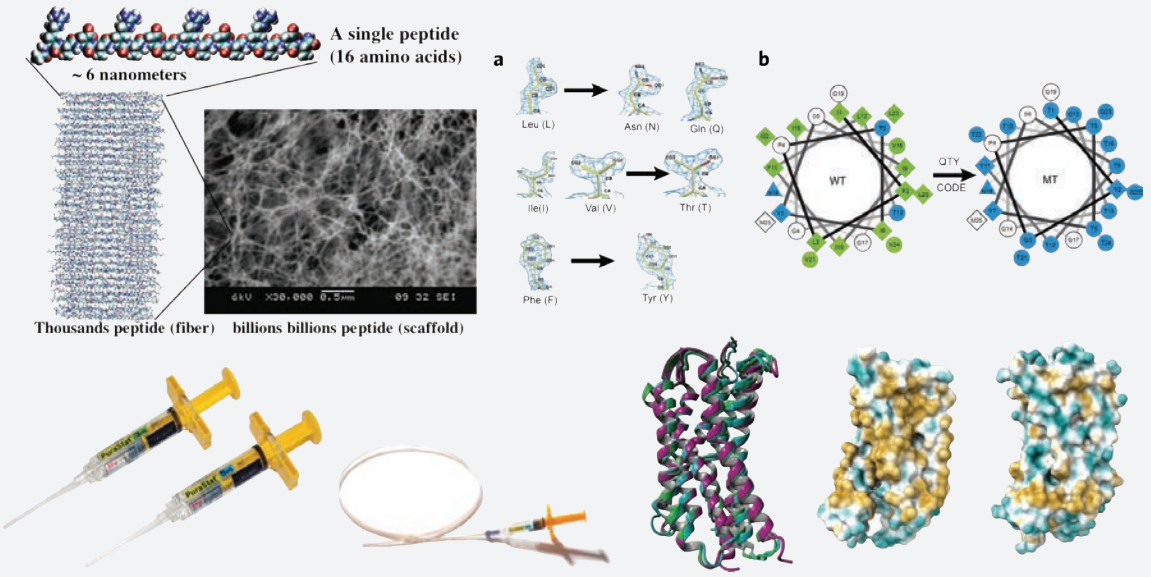

Figure 7. **Some of my research activities.** *(Left panel) I discovered the first self-assembling peptide EAK16 from a yeast protein Zuotin in 1990. Because the work was not funded by any grants, Alex Rich remarked, "You have made an unauthorized scientific discovery." It is very satisfying to generate new scientific knowledge, from knowing nothing at all 1990 to nearly fully understanding the mechanism of self-assembly in 2005. The knowledge has also been translated into useful medical products. Several self-assembling peptide nanofiber scaffold hydrogel products are used in medicine for surgical uses (stopping bleeding in a few seconds), and for accelerating healing of wounds such as diabetic ulcers and bedsores. (Right panel) In 2011, I conceived a simple QTY code to make water-insoluble integral membrane proteins water-soluble. The QTY code is based on three basic chemistry facts: 1) all 20 amino acids are found in alpha-helix, 2) Several amino acids share remarkable structural similarity despite their water-soluble properties: L ↔ Q, I/V ↔ T, and F ↔ Y, thus the QTY code. 3) There are three chemically distinct alpha-helices with nearly identical structures: (i) hydrophilic helix, (ii) hydrophobic helix and (iii) amphiphilic helix. They all have a 1.5 Å rise per amino acid, a 100° rotation per amino acid, 3.6 amino acids per helical turn, a 5.4 Å rise per helical turn, and the key feature, i.e. each NH- group of each amino acid forms an H-bond with the -C=O group of the amino acid 4 residues away, i, i+4. The QTY code has been used to design water-soluble membrane proteins for various biotechnological applications. a) Hydrophobic amino acids L, I, V, F can be replaced by hydrophilic amino acids Q, T, Y because they share similar molecular structures. b) A hydrophobic alpha-helix (green color) becomes a hydrophilic alpha-helix after applying the QTY code.*

water-soluble variants of previously water-insoluble and perhaps aggregated proteins, including amyloids (Figure 7b).

The QTY code is based on two key molecular structural facts: 1) all amino acids are found in natural alpha-helices regardless of their chemical properties; 2) several amino acids share striking structural similarities despite their very different chemical properties, for example, glutamine (Q) *vs* Leucine (L); Threonine (T) *vs* Valine (V) and Isoleucine (I); and Tyrosine (Y) *vs* Phenylalanine (F). The QTY code systematically replaces water-insoluble amino acids (L, V, I, and F) with water-soluble amino acids (Q, T, and Y) in transmembrane α-helices. Thus, it changes the water-insoluble form of membrane proteins, including GPCRs, into a water-soluble form. Despite substantial transmembrane domain changes, the QTY variants maintain stable structure and ligand-binding activities. My lab has been successful in designing water-soluble variants of membrane proteins.

A FEW FINAL WORDS

"In school you are judged by the questions you answer; in real life, you are judged by the questions you ask."

Robert Langer
MIT Professor

Life is full of ups and downs. Like the uneven edges of a fractal, life's journey is never entirely smooth. As long as I am optimistic and have a long-term outlook, things will look up even at the bottom. I am irrepressible and sometimes even irrationally exuberant about my scientific research and life. I have been able to pursue what I have been really curious about. I tell people that I have been paid to play.

I am now at MIT Media Lab, Massachusetts Institute of Technology. My current research focuses on designs of biological molecules, particularly proteins and peptides that are

Figure 8. **My lab members in 2000s.** *My lab pursued diverse scientific research endeavors including: i) self-assembling peptide nanofiber hydrogels for regenerative medicine and molecular delivery, ii) lipid-like peptides for stabilize membrane proteins and as molecular delivery system; and iii) invention of the QTY code to design water-insoluble integral membrane proteins to become water-soluble. a) Members of my Laboratory of Molecular Self-Assembly in 2005 in front of the classic MIT Killian Court, b) at the 500 Technology Square in 2006. c) In front of the Frank Gehry-designed MIT Stata Center in 2007. d) In 2012, in front of the Media Lab Wiesner Building designed by I.M. Pei who designed 3 letters M.I.T. into the building architecture.*

short fragment of proteins. I obtained my B.S in Biochemistry from Sichuan University and earned my Ph.D. in Biochemistry & Molecular Biology from University of California at Santa Barbara. I was an American Cancer Society Postdoctoral Fellow and a Whitaker Foundation Investigator at MIT. I was a 2003 Fellow of Japan Society for Promotion of Science (JSPS fellow). My work of designer self-assembling peptide scaffold won 2004 R&D100 award. I won a 2006 Guggenheim Fellowship and spent academic sabbatical in University of Cambridge, Cambridge, UK. I won 2006 Wilhelm Exner Medal of Austria (Figure 9a). I was elected to Austrian Academy of Sciences in 2010 (Figure 9b), elected to American Institute of Medical and Biological Engineering in 2011, elected to US National Academy of Inventors in 2013, elected to the European Academy of Science and Arts in 2021, won the 2020 Emil Thomas Kaiser Award from the Protein Society. I published >180 scientific papers that have been cited over 36,000 with h-index 91. I am also a co-founder and board member of Molecular Frontiers Foundation. Molecular Frontiers Foundation organizes Molecular Frontiers Symposia in Sweden and around the world (Figure 10). Because of my repeated good experience of asking questions that changed my life for better, I helped to establish the Molecular Frontiers Inquiry Prize that encourages young people to ask big and good scientific questions about nature without accomplish any research projects. The selected winners are awarded the Molecular Frontiers Inquiry Prize.

I also co-founded a startup company 3DMatrix to use self-assembling peptide scaffold hydrogel for accelerate wound healing, and uses in a wide range of surgical applications. I also founded other biotech startups, OH_2 Laboratories to generate therapeutic monoclonal antibodies using the

Figure 9. **Austrian connection.** *I have been fascinated by the musical genius and magician Mozart who could simply "download" from his mind to paper his over 800 magnificent music compositions without corrections. I am extremely enthusiastic for Mozart's timeless music. I have been to Vienna countless times. I became a close friend of the leading scientist and unique artist Dr. Uwe Sleytr, who has introduced me to many scientists including Hans Tuppy and other Austrian academicians. a) 2006. After I received the Wilhelm Exner Medal of Austria, I met with Austrian President Heinz Fischer who insisted that I sit in his chair before going to lunch with him and his wife Margit Fischer. b) Induction into the Austrian Academy of Sciences in Vienna, May 10, 2010.*

Figure 10. **The Molecular Frontiers Symposia at the Royal Swedish Academy of Sciences in Stockholm, Sweden.** *Since 2007, Molecular Frontiers Foundation has organized many Molecular Frontiers Symposia in Stockholm, Sweden. Pictured are from the symposia in a) 2008, and b) 2013. Molecular Frontiers Symposia have been held around the world in Europe, Japan, South Korea, Singapore, India and the United States.*

Figure 11. **With my wife Dorrie Langsley.** *a) With Dorrie in the home of Uwe and Henny Sleytr, Vienna, Austria in August 2015 (Photo taken by Uwe Sleytr). Dorrie and I share a great deal in common despite growing up in completely opposite cultures, environments, societies and countries. Shared human nature transcends family background, culture, and socio-economic origins. Dorrie and I married in Vienna, Austria on December 17 (1217, a prime number), 2016. b) With Dorrie in Lakewood, Colorado, July 2022 (Photo taken by Jill Wilcox). Our personal bond has grown from hydrogen bond to ionic bond to covalent bond.*

QTY code designer water-soluble GPCR variants, and 611 Therapeutics to treating stroke using the designer self-assembling peptide scaffold hydrogel to repair stroke-damaged brain through reconnecting neurons.

After >34 years at MIT since June 1988, I am still having a lot of fun, conceiving new scientific ideas, doing the cutting edge of scientific research, making new discoveries, and inventing new technologies. Through asking good questions, I have already won my biggest prize of my life, my dear, and wonderful wife Dorrie Langsley who is beautiful, very warm, extremely supportive, and understanding. Despite the fact that we come from totally different backgrounds, educational systems, and grew up in completely different environments (Dorrie in capitalist United States and me in communist China), we share a lot in common and enjoy reading the same books, watching the same films, traveling and meeting family members, good friends, and close colleagues around the world. Together, we are a very fortunate and happy couple and I am the happiest man on earth (Figure 11)!

Box 1. Asking good questions has significantly changed the lives of several students for the better.

Here are a few examples of students who asked good questions, which led to changes in their lives for the better, that I personally experienced and observed:

1) I saw a conference poster in October 1982 at UCSB Chemistry Department classroom there that Alexander Rich was to schedule to give an opening lecture, I paid my own airfare from Santa Barbara to participate the conference of "*Conversation in Biomolecular Stereodynamics III*" in June 1983 at the State University of New York at Albany. During the conference, I sat in the front row and taped almost everyone's talk. Since I was also very close to the microphone, I asked questions to most speakers. Most of my questions are due to my lack of frontier scientific knowledge that can be easily addressed. But because my lack of some scientific knowledge, some of my questions were unexpected and very good questions, several speakers had to think about and some of them could not answer my questions. That caught attention of many leading scientists of the day including Professor Alexander Rich. During the break, I approached Alex Rich and asked if he would accept me as a postdoc after I earn my Ph.D. at UCSB, he immediately said yes without hesitation. He told me to write him when the time is near completing my Ph.D. I followed his advice and wrote him in 1986. He advised and guided me to write a fellowship application, I did and obtained an American Cancer Society fellowship and arrived to Alex Rich's lab in June 1988. From asking a lot of questions at that one meeting, I got to know many leading scientists and kept in touch with them including several future Nobel laureates.
2) In 1991, a delegation of US National Academy of Sciences that include the future Nobel laureate Robert Horvitz of MIT, David Anderson of Caltech, Lawrence Bogorad of Harvard University, Mark Fishman of Harvard Medical School-Massachusetts General Hospital, Helen Blau of Stanford University, had a joint scientific symposium with a delegation of Chinese Academy of Science (CAS) including CAS Academician Lin Qishui, Qiang Boqing and others in the CAS Institute of Biochemistry in Shanghai. During the symposium, a young female student repeatedly asked good questions to many speakers. That immediately caught the attention of Professor David Anderson and others. We were all very impressed. After the symposium, Professor Anderson had a chat with the young student and invited her to apply for graduate program at Caltech. She did and was accepted by Caltech to be a graduate student in 1991.
3) At a scientific symposium my colleague Zhao Xiaojun and I organized in Chengdu, Sichuan in June 2006, a female student asked a lot of good questions to several speakers. That caught attention of Professor Sir Alan Fersht. After chatting with the student during the symposium, Alan Fersht invited the student to apply for University of Cambridge. The student later went to the University of Cambridge to carry out graduate studies. Asking questions changed her life for much better.
4) In March 2021, an undergraduate student wrote me, out of the blue, and asked if she can do remote intern work on some bioinformatic projects. I replied to her and soon invited her to have a Zoom meeting. Since then, she has been working with me on a few projects to use AlphaFold2 to predict membrane protein structures, especially the water-soluble QTY variants. The crystal or CryoEM determined structures of native membrane protein and AlphaFold2 predicted water-soluble variants share remarkable similarity despite 50% sequence differences in the transmembrane helix domain. She has now published five scientific papers with my lab including two first-author papers. These papers will make her more successful in applying for the best graduate schools in the world.

Box 2. Write letters to ask leading scientific experts about leukemia.

In 1987 soon after my son was diagnosed acute lymphoblastic leukemia (ALL), I searched and read a lot of scientific and medical articles and books about ALL. (As it is often said, the motivation is the best teacher). I also wrote letters to many leading scientists around the world, but only a few replied. Those who wrote me back included George Klein of Karolinska Institute and Stephen Sallan, then the Director of the Jimmy Fund of the Dana Farber Cancer Institute in Boston. I was quite moved that several famous scientists and physicians took the time to write to an unknown graduate student regarding his son's ALL. George Klein not only wrote me a lengthy letter, but he also sent me many of his publications on the molecular basis of leukemia and chromosome translocations that result in leukemia. Dr. Sallan also wrote me back. After I obtained the fellowship from the American Cancer Society, I wrote Dr. Sallan again and asked if we could have a phone call. He wrote me back and agreed to have a phone call with me. During the call, I told him I would be coming to MIT to work with Alexander Rich as an ACS Fellow in June 1988. I asked him if he would be willing to be my son's physician. To my great surprise, he agreed. During our first meeting at the Jimmy Fund, he brought a younger physician Dr. Eric Larson who was to take charge of my son's treatment under Dr. Sallan's supervision. When my son was in the Children's Hospital for a possible relapse, he came to see my son several times. Dr. Sallan's expertise on ALL ensured that my son received the latest and best treatment. My son has been cured of ALL ever since, and today is heathy and working as a software consultant.

Box 3. Organizing small workshops.

I asked what is the best way to promote a brand-new field of research, the best answer is to bring people from diverse fields together under one roof, where they can openly discuss and cross-fertilize ideas related to the new science. This should ideally take place in a relaxed and somewhat isolated setting. I did precisely that. I co-organized with Amaila Aggeli, Neville Boden, Michael Hecht, William DeGrado and Joel Schneider five small biannual workshops (1999, 2001, 2003, 2005, 2007) at the Capsis Hotel in Crete, Greece (Figure 12). We invited leading scientists in their own fields to mix them in an intimately marvelous environment on a beautiful Greek island. There, these leading scientists spent lot of time with young, energetic students, postdocs, and researchers. These workshops had a significant impact, and accelerated the development of an emerging field. All participants greatly enjoyed the experience, and hold fond memories of these meetings even after many years. I also co-organized a workshop with Andreas Mershin and Yiannis Koukas on another beautiful Greek Island Mykonos (2009) (Figure 13a). Later I also co-organized small meetings with Dr. Mouad Lamrani, in Le Mans, France (2013) (Figure 13b) and Geneva, Switzerland (2016, 2018).

Figure 12. **Self-Assembling Peptides and Proteins workshops in Crete, Greece.** *I organized, together with colleagues Amalia Aggeli, Neville Boden, Michael Hecht, William DeGrado and Joel Schneider, five small and intimate workshops, held in 1999, 2001, 2003, 2005 and 2007, to encourage interdisciplinary interactions and collaborations. These workshops brought leading scientists from diverse fields to pursue an emerging field of self-assembling peptides and proteins. Many undergraduate and graduate students and young scientists who attended later become leaders in their fields.*

Figure 13. **Other protein workshops.** *a) After I changed my research direction to work on membrane proteins, Dr. Andreas Mershin, Yiannis Koukas and I organized a workshop in Mykonos, Greece on protein structures and biotechnology in 2009. b) Dr. Mouad Lamrani and I organized meetings in Le Mans, France (2013) and Geneva, Switzerland (2016 and 2018). The 2020 and 2022 workshops were cancelled due to the Covid-19 pandemic.*

Box 4. Molecular Frontiers Foundation—Prizes for asking questions.

In 2005, I gave a talk at the American Chemical Society meeting in San Diego, California. Bengt Nordén was also there and heard my talk on colloidal peptides. He asked me if I would share my slides with him. I immediately agreed without knowing who he was. After it turned out, Bengt Nordén knew my mentor Alexander Rich very well, and we knew a lot of other people in common, including his close colleague Carl-Ivar Brändén. During dinner together with Andreas Mershin and Horst Vogel, we discussed the major problems of chemistry education and how to improve it. We all agreed that it is most important to encourage young people to study science in general, and particularly chemistry, to find a way to make learning chemistry fun. We decided to form a foundation for the endeavor. After much discussion, we called it the Molecular Frontiers Foundation. We made a list of leading scientists to become members of the Scientific Advisory Board. We decided that the best way to go forward would be to organize an annual Molecular Frontiers Symposium. We would invite Nobel laureates and leading scientists to Stockholm and other symposia around the world, to present their work to high school student audiences. I also suggested that we establish the Molecular Frontiers Inquiry Prize to challenge students under 18 to ask scientific questions since good questions often lead to good scientific research. We would give the Inquiry Prize for the best questions. This is the first time a prize has been given to young people solely for asking good scientific questions. We award the prize to five boys and five girls. This levels the global playing field since young people from anywhere in the world can be recognized for the questions they ask, rather than for their answers. Since its inception, more than 100 gold-coated medals, and small iPads, have been awarded to those students who asked the best questions. In contrast to my demotions for asking questions in the army so long ago, we reward the questioners.

After the discussion of the Molecular Frontiers Foundation, Bengt Nordén also invited me to participate the joint Nobel Symposia in Sweden (Figure 14a). During the same week, I was invited to participate the George and Eva Klein's 2×80 birthday symposium at the Karolinska Institute (Figure 14b). It was a tremendous honor to participate such symposia and meet the leading scientists in the world. As the title of this article says, "Always ask questions."

Figure 14. a) **The joint Nobel Symposium at Sånga Säby in Sweden and the George and Eva Klein Symposium at the Karolinska Institue.** *After I met Dr. Bengt Nordén at the American Chemical Society meeting in San Diego, I was invited to participate in the joint Nobel Symposium in a small village, Sånga Säby, Sweden, in May 2005 where many Nobel laureates and future Nobel laureates presented their latest scientific research; b) Celebrating the 2 x 80th birthday of George Klein and Eva Klein at the Karolinska Institute in Stockholm, Sweden, 2015. Several Nobel laureates and future Nobel laureates gave talks on their latest scientific research.*

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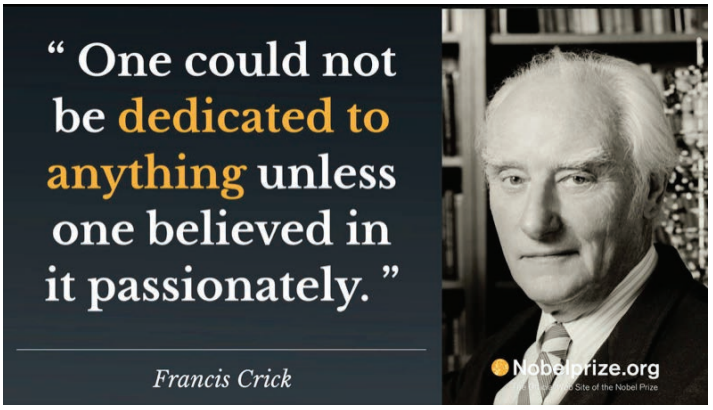
The White Horse (Mr. Sai Weng lost his horse, ~200 BC, China)

Mr. Sai Weng had a strong son and a nice horse. The villagers were envious of Mr. Sai, and told him how fortunate he was. One day, his horse disappeared. The villagers all felt very sorry for Mr. Sai, but he said, "that is life, the loss might turn out to be a good thing." A few weeks later, the horse returned home. The horse was not only healthy—he also brought another beautiful horse along. The villagers were again envious of Mr. Sai and told him how fortunate he was. But Mr. Sai said, "'Good luck' might bring about misfortune in the end." Indeed, a few days later when his son was riding the new horse, he fell off and broke his leg. The villagers were very sorry. Said Mr. Sai, "The broken leg may turn out to be a good thing." Soon afterward a war started between Mr. Sai's country and a neighboring country, and all healthy and able young men were drafted into the army. Since Mr. Sai's son had a broken leg, he was not drafted into the army. Almost all of the young men from the village died or seriously injured during the war. However, Mr. Sai's son's broken leg eventually healed, and he lived. The villagers were again envious of Mr. Sai and told him how lucky he was to still have his son; Mr. Sai said, "that is life."

The wisdom of the story: life has always ups and downs. Sometimes bad fortune can turn into good luck, and vice versa. https://www.i-kicoaching.com/en/the-story-of-the-old-chinese-farmer-and-his-horse-by-lao-tzu/



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