As people look back on their personal journeys, growing as individuals and in their careers, how many of us had dreams that were big enough for all the challenges and opportunities we would face?

My childhood was filled with the wonders of living in a small town in the mountains of Colorado, where hiking, fishing, sledding in winter, walking on rocks to cross a stream to go to junior high, and in general roaming the surrounding hills, are my childhood memories. Perhaps these are strange memories for a girl whose parents came from China to the US for graduate school; but because of wars they had lived through in China, and then the death of my father when my siblings and I were 7 weeks old, 6 and 4 years old respectively, my mom moved us to Durango. Durango was a town of 10,000 people, mainly a mix of ranchers and others who also loved being outdoors whether to ski or just to enjoy nature. Mom selected Durango because as a young widow with three children, with most of our family an ocean away, she found it to be the ideal combination of a small town community coupled with a state college whose faculty provided an educational and cultural environment more commensurate with a less isolated and larger city.

My mom was an amazing person who lived out her Christian faith through incredible caring for those less fortunate than she, despite the many challenges she faced as a widow raising 3 young kids, relatively poor due not just to my dad’s death but to initial significant racial prejudice (despite her two masters degrees and a doctorate). Our family had two mottos: “One for all, and all for one!” à la “The Three Musketeers”; the other that we kids shared only amongst ourselves was, “You have to be used to being embarrassed to be a Liu,” due to periodic mortifications such as pushing our mom in our old car down the sloping street to get it started on cold wintry days, while classmates walked by. Mom was incredibly devoted to us, her children, always making us feel that any dream was achievable. Even though money was tight, we felt rich in opportunities and blessings, in part because of Mom’s generosity to others and because music lessons on two instruments each were a given.

Most importantly, we children were raised knowing that “to whom much is given, much is expected”. That is, we knew that our purpose in life was to share God’s love with others, by helping them, both through our life’s work and through reaching out and giving to those less fortunate than we. There were only 3 Chinese families in town, including ours; the others ran a restaurant and a laundery, but perhaps their parents, like Mom (who although she retired with the rank of Professor), had initially taken work way beneath their educational accomplishments in order to provide for their children. To emphasize our responsibility to be good stewards of our opportunities, Mom would remind us that our great grandfather was a scholar of the Hanlin Academy, the highest and most exclusive level of scholarship in Imperial China. Growing up in a place where being different was both remarked upon and taken for granted (due to the great diversity of backgrounds and ethnicities—ranchers, skiers, hippies, Native Americans, Hispanics, etc.) helped prepare me to be willing to, “Take the road less travelled” as Robert Frost would say, throughout my schooling and career. This included sometimes marching to the beat of a different drummer, whether that meant taking an educational or career path that was not necessarily the standard one, or to stay true to the core values with which I was raised, despite worldly pressures.

Durango is the kind of town where people find creative solutions to problems and challenges. So although the high school didn’t yet offer Advanced Placement classes (can you imagine!), I was allowed to take courses at the state college in town, hiking or hitchhiking up the hill during lunchtime to spend the afternoon at Fort Lewis College taking courses starting from when I was 13 years old. (For you cycling enthusiasts, Fort Lewis College’s cycling team has won the national title 24 times, probably due in some part to the school being located at nearly 7,000 feet in elevation).

Going against the grain continued in college, when I turned down offers to Yale and Princeton—which were only in their 5th year of admitting women() (with my sister already at Radcliffe/ Harvard) to attend Colorado College, in large part due to a full scholarship offered by an amazing foundation, the Boettcher Foundation, designed to keep students from Colorado within the state for college, rather than going away to Ivy League schools. Colorado College has an academic program where you study only one subject at a time, for 3 ½ weeks. After each final exam, is a short “Block Break” where students...
spend a half week either vacationing or getting a jump start on
the reading for the next course. As you can imagine, courses
like organic chemistry are extremely challenging because you
have to fit in all the lectures and labs into less than a month. But
an archeology class could go away from campus to a dig. And
when studying foreign languages, the immersion is so great that
one starts dreaming in the foreign language. (When I was
named by Discover magazine as one of the 50 "Most
Important Women in Science" I discovered that 3 of us selected
from all the women in all scientific fields in the USA were
alumnae of tiny CC—with a freshman class each year then of
around 400!) At CC, I discovered both biochemistry and
immunology, where the mechanisms of chemical reactions
and cellular activation were fascinating. At the same time, the
environment enabled students to maintain and develop their
other interests. Some of the best musicians were my fellow
chemistry majors, so we formed a woodwind quintet (with
me on flute), known as the "Keytones" or rather, the "Ketones".

When I had completed all the required courses for gradu-
a tion a year early (due to transferring credits from Fort Lewis
College from my time in high school), I was blessed to
received another amazing scholarship, this one from the
Rotary Foundation, to continue studying piano (which I had
started at the ripe age of 5) at a conservatory in Paris, France.
What an experience for a young girl from a town of 10,000
people in the "Wild Wild West" to be plopped into the middle
of Paris, living in a boarding house run by nuns filled with
girls studying at the various conservatories and ballet schools
in Paris, and exploring the museums and amazing cultural
offerings of Paris when not practicing the piano. The kindness
shown to me by so many Rotarian families, many of whom
I have remained in touch with—and in turn have hosted their
descendants, opened my heart and eyes to the world: to
shared humanity, to other cultures and ways of thinking,
and to the incredible achievements of humankind. I applied
to medical school from Paris (do you know how challenging it
was to type on a French keyboard in the days before
"white-out" and "cut-and-paste on a computer"?) and ended up
deciding on Harvard Medical School.

Although I had thought medical school, particularly at
Harvard, was primarily a way for me to enter the world of
biomedical research, clinical care of patients was enjoyable
and challenging. And so I completed internship and residency
in Internal Medicine at Massachusetts General Hospital, one
of Harvard’s main hospitals. I went on to complete my clinical
fellowship in Endocrinology and Metabolism also at MGH,
becoming board certified in both Internal Medicine and
Endocrinology and Metabolism. Endocrinology intrigued me
because of the exquisite feedback loops of the systems and the
nature of the mechanisms by which hormones activate cellular
processes. In addition, many endocrinological disorders have
an immune-based etiology. I combined the two fields of
endocrinology and immunology by obtaining a Physician
Scientist NIH 5-year grant (with a near-perfect priority
score) that enabled my initial faculty position—at Harvard—a
lowly appointment as an Instructor.

During my fellowship, and in order to gain more expertise
and research skills in immunology, I split my time by also
going across the river as a Visiting Scientist at MIT, working
with Herman Eisen, known for his seminal work on antibody
binding, elucidating the T cell receptor, and of course his
influential textbook, General Immunology. His love of science
was such that he was still working on a manuscript (published
posthumously in Cell) on the day he died, aged 96, while on
his way to the gym. In Herman’s lab, I had first-author
publications in Science, JCI, and PNAS, co-authored a Nature
paper, and had my first patent filed (on bi-specific
antibodies to activate T cells to kill tumor cells, either Ab-Ab
conjugates or Hormone-Ab conjugates). The first bispecific
antibody treatment for human cancer was approved by the
FDA in 2014, 29 years after my Science paper was published,
which gives me hope for DNA vaccines! The other papers
dealt with serine esterase in Cytolytic T Lymphocytes, in
which Mark Pasternak as the first author showed that granzyme
was a mechanism by which CTLs kill target cells. The
JCI paper was published with colleague Theresa Liu from
Biogen about recombinant soluble CD4, which was being
tested for its ability to block HIV infection of CD4+ T cells.

People assumed we were sisters, even though we are not
related.

During internship at MGH, I met the love of my life (is it
OK to mention things like this in a professional journal?),
Robert Johnson, who had come to Boston after receiving his
MD-PhD at the University of Pennsylvania, “to find out what
all the fuss about Harvard was”, in his own words. We
married at a small chateau in the Loire valley of France, Le
Gué Pèan, or Le Château d’Amoureuses Légendes ("The
castle of love legends") since a former queen of France and her lover
used to stay there, as did Chopin and Georges Sands—one of
Chopin’s pianos is still there. Fortunately for us, we have
small families and the French franc was weak, so the
Marquis de Kéguelin de Rozières, our host, was able to put
up both our families at the chateau as well.

Since Peggy is a nickname for Margaret, you can imagine
that I would at times be confused with Peggy Johnston, the
HIV expert, by people who knew my husband, but not me.
But of course I had kept my own name, not only because of
my professional life, but because I thought that people who
hadn’t initially met me in person might not expect a Chinese
face when meeting a Margaret Johnson. This dates me, but for
those reading this who are young or not aware of the actual
situation in the US, laws prohibiting marriage between a white
person and someone of another race existed until 1967 when
the US Supreme Court ruled that such laws were unconstitu-
tional. And, although Robert and I married in 1983, well after
that, South Carolina and Alabama didn’t change their state
constitutions until 1998 and 2000, respectively, to take out the
language prohibiting miscegenation. But I digress....

Robert took only 3 years to complete the normal 6 years of
internship, residency and fellowship, due to his extra degree,
then became a Howard Hughes investigator, and Assistant
Professor at Harvard Med. (MGH). The Howard Hughes
Institute asked him to move to UPenn as they wanted to start
an HHMI there, so I made plans to join the UPenn Department
of Medicine and move the remaining years of my NIH funding
with me. However the recombinant DNA and biotech revolution
had just begun, and coincidentally the chair of my department at
MGH/Harvard, Mike Rosenblatt, was recruited to be the VP of
Research at Merck by Ed Scolnick, the Merck President of Research, who himself had been recruited from the NCI by the new CEO of Merck, Roy Vagelos, who like Mike, Ed, and now me had trained at MGH. Those were Merck’s glory days when it was “America’s most admired company” 7 years in a row. And some prominent scientists had left academia to go to biotechs. So as a young scientist who would have set up my first independent lab, I realized that my resources would be significantly greater if I took a position at Merck rather than at UPenn, and my team would include PhD scientists and technicians with post-graduate degrees. This was important now that biotech meant that your success as a scientist would depend on your speed (i.e., person-power), not just your (hoped-for) brilliance. So I asked the NIH to put my grant on hold—even though leaving academia went against everything that I had been culturally raised to value as a career (both my parents were university/college faculty), and despite my medical school aim of being a “triple-threat”, someone who saw patients, did research, and taught. Once I got to Merck, and realized how quickly my research could progress, I wondered why I had agonized over the decision for so long (nearly a year of living still in Boston, while Robert had already moved to Philadelphia).

At Merck, I was privileged to have Maurice Hilleman, the legendary vaccinologist who developed more than 40 vaccines, as an inspiration and friend. Despite his gruff ways, he was incredibly kind, and we shared a Western small-town heritage. In my career he was one of the few people who actively (and with great wisdom) mentored me. My first hires included John Donnelly, Jeff Ulmer, and John Shiver as project leaders. We demonstrated the mechanism of Merck’s new Haemophilus influenzae b vaccine (showing that the outer membrane protein complex was an adjuvant, not simply a carrier protein, thus providing an explanation for why Merck’s vaccine was immunogenic in infants of a younger age than other conjugate vaccines). We also worked on bifunctional antibody activation of T cells and sought ways, including utilizing a pseudomonas exotoxin fusion protein to access the class I processing pathway. The goal was to activate cytolytic T cells for both prophylactic vaccines against infectious diseases and cancer immunotherapy.

Thus we were primed, (pun intended), when Phil Felgner and his colleagues from Vical visited Merck, presenting their work demonstrating that in vivo injection of plasmid DNA, “naked DNA” without the use of transfecting agents or electroporation, resulted in transfection of the cells, and expression of the encoded protein. We were interested in seeing whether this could be used as a way to generate cytolytic T lymphocytes (CTLs) since CTLs generally can only recognize epitopes expressed on MHC Class I molecules following in situ production of a protein, meaning that proteins injected in many vaccines wouldn’t generate CTLs even though antibodies could be generated.

This led to our publication, with our Vical colleagues as co-authors, in Science in March of 1993 of results showing that direct injection of plasmid DNA encoding influenza nucleoprotein (NP) could generate CTLs and protect mice from challenge with a heterosubtypic strain of influenza (H3N2), one that arose 34 years later than the strain (H1N1) from which the gene was taken. We also showed that by encoding influenza hemagglutinin (HA), DNA vaccines could elicit antibodies in mice, ferrets, and rhesus monkeys. Our work also helped our Vical collaborators demonstrate enablement for the patents that they had filed on DNA vaccines. We at Merck were rewarded with $1 for each patent filed.

The time leading up to the Science publication was an anxious time because when we had presented our protection and mechanistic data a few months earlier at a 1992 Cold Spring Harbor meeting (with manuscripts published in a “Vaccines 93” CSH publication), we discovered that two other groups had some data that were more preliminary (protection in chickens and mice using a retroviral vector then plasmid, likely antibody-based, and antibody responses against HIV Env protein), but still using DNA. We were exhilarated when our Science paper was indeed the first and most comprehensive publication, meriting a Science commentary by Jon Cohen and coverage by the New York Times and many media outlets.

The demonstration that this technology could provide protection against a different strain of influenza and generate both CTLs and antibodies raised hopes for a universal flu vaccine and other vaccines that might need or benefit from cellular immunity (such as Tb, HIV, and cancer immunotherapy) or antibodies against antigens that were difficult to produce (such as HIV Env). It was a robust platform technology that had the potential to address many human and veterinary diseases. Moreover, the technology appeared to be simple enough for for global health applications, where characteristics such as thermostability and relatively low manufacturing costs were added potential attributes.

Over the next few years, we extended the pre-clinical efficacy models to a number of diseases and figured out some of the crucial issues, such as determining that cross-presentation of antigen could occur, (since myocytes aren’t professional antigen-presenting cells), improved the expression vectors, did various non-human primate studies with Norm Letvin at Harvard, and prepared for a Phase I study in influenza, the first DNA vaccine to go into non-infected healthy humans. Unfortunately, the decision was made to clinically test a hemagglutinin-encoding DNA vaccine for the generation of antibody responses, such as a traditional flu vaccine would generate. This was a disappointment to those of us who had hoped that the clinical study would be designed to validate in humans the pre-clinical demonstration that cellular responses against epitopes from a conserved influenza protein encoded by DNA would provide cross-strain protection and thus the DNA vaccine would be a universal flu vaccine.

Ours was the first DNA vaccine to be tested in healthy humans, as well as the first test of a DNA vaccine with an aluminum adjuvant in humans. Although the study did not meet its primary endpoint of showing HI antibodies superior to those induced by a conventional flu vaccine, it did show that priming with DNA followed by protein boost elicited functional (HI) antibodies in humans. While not the study we had originally envisioned for testing the ability of a DNA vaccine to generate CTL, its results both showed that DNA vaccines were safe in healthy individuals, and set the stage for several further studies of prime boost such as has been done for HIV vaccination in humans. This included HVTN 049, which showed that
HIV Env DNA was both an effective way to generate CD4 + T cell help for subsequent boosts, and an effective prime for a subsequent boost with a protein version of HIV Env. I was recruited away from Merck, and left, in part, due to disappointment with the direction of the program once the primary focus was changed (to antibody responses) by the development, rather than research, group. The results were presented by Mary Lou Clements-Mann, the lead investigator from Johns Hopkins. But in a great tragedy, she was killed in the crash of Swiss Air flight 111; the results were never published.

Nevertheless, the trial was: 1) an important demonstration of the safety of DNA vaccines in normal healthy individuals (addressing key concerns related to the then-unanswered questions of whether a DNA vaccine would cause auto-immunity or integrate into human chromosomes), 2) demonstrated the use of DNA with an alum adjuvant, and 3) showed the increased potency of a DNA vaccine prime followed by a protein boost.

Meanwhile I was settling into my role as Vice-President of Vaccines at Chiron, a biotech company. This was soon expanded to Vice-President of Vaccines and Gene Therapy as I gained responsibility for the gene therapy efforts that Chiron assumed by its purchase of the company Viagene. At Chiron our projects included HIV and HCV vaccines and various related technologies (DNA vaccines, adjuvants, replicons), as well as gene therapy, notably for hemophilia A. Then priorities changed with a new CEO, and Chiron decided to focus more on combichem (and not gene therapy); I left, leaving behind a strengthened vaccine group in the US.

The Bill & Melinda Gates Foundation asked me to become their Senior Advisor in Vaccinology. This was a heady time for all vaccine researchers as the Foundation’s recognition of the importance of vaccines injected new prioritization for vaccines for poor people, in poor countries, and put huge financial resources into both R&D and vaccine access. The position was a wonderful way for me to become more involved in global health since heretofore, I had really focused on vaccine R&D per se, although because DNA vaccines were thought to be a potential platform technology that could be used globally, and because most of my personal work was on HIV and influenza, I had always been somewhat involved in global health vaccine issues. I requested that I not be full-time because I didn’t want to be completely separate from the R&D process, so I also joined the board of a French biotech company, Transgene, as the Vice-Chair.

During that time I was invited by the Nobel Committee to give a lecture in the Karolinska Research Lecture series in Stockholm. This was followed by an appointment as a Visiting, then Foreign Adjunct Professor appointment, at the Karolinska Institutet where I have worked closely with Britta Wahren, a pioneer in many areas, including DNA vaccines. I was thrilled to again become involved in teaching, now graduate students and post-docs, and was impressed to find out that the Nordic stereotypes were somewhat true, when one of the students spent all week working hard, then cross-country skied between towns over the weekend. This past year, I was extremely honored to receive an honorary Doctorate of Medicine from the Karolinska Institutet, in a white tie ceremony held in the Stockholm City Hall where the Nobel banquet is held, complete with cannons firing, a special hat and ring, and amazing colleagues.

Splitting my time between the Gates Foundation and Transgene (where my apartment was incredibly located adjacent to the picturesque section of Strasbourg, “La Petite France”) opened my eyes to a different career path, one where I divide my time between institutions and efforts, rather than being at a single institution. I realized that I most enjoyed the excitement of using new technologies in an effort to generate new vaccines and immunotherapies to decrease suffering. So after a satisfying time at the Gates Foundation, I entered my current phase where I split my time between advising biotech companies, pharma, and investment firms on platform technologies and strategies for developing vaccines for infectious diseases and therapies for cancer, sitting on boards (both scientific and corporate) working with international agencies (I had developed the Terms of Reference for the WHO Initiative for Vaccine Research, and was the Chair of the Scientific Advisory Group and then the Vice Chair of the Board of Trustees, for the International Vaccine Institute, established by UNDP, in Seoul Korea, etc.), and have adjunct appointments at the Karolinska Institutet and UCSF School of Medicine.

I joke that for the past fifteen years, I must have thought that because cities starting with an S are near one another alphabetically, that they seemed reasonable as concomitant work places, because I have spent most of my time in: Seattle, Strasbourg, Stockholm, Seoul, and Shanghai, while living near, and sometime working in, San Francisco.

Was it part of my dream to be known as “The Mother of DNA Vaccines” (https://www.washingtontimes.com/news/2015/mar/14/durango-native-margaret-liu-is-the-mother-of-dna-v/), and to spend most of my career involved in research and global health, rather than in patient care or in personally developing the technologies that I pioneered, both bspecific antibodies and DNA vaccines into products? The conclusion, I think, is that one should delight in the many unexpected opportunities that arise, and be eager to embrace a changing world, all in the effort to ease the suffering of our fellow humans, and to experience the joy of working with incredibly committed and brilliant colleagues.

Notes on contributor

Margaret Ann Liu. Dr. Liu obtained an M.D. from Harvard Medical School, a B.A. in Chemistry, summa cum laude, from Colorado College, and passed the Epreuve pour le Diplôme d’Enseignement, à l’unanimité (judges’ unanimous decision), in piano from the École Normale de Musique de Paris. She completed Internship and Residency in Internal Medicine and a Fellowship in Endocrinology, all at Massachusetts General Hospital/Harvard Medical School. Previous visiting, faculty, and adjunct faculty appointments were at the Massachusetts Institute of Technology, Harvard Medical School, and The University of Pennsylvania, respectively. Dr. Liu received an NIH Physician Scientist Award, and served as Senior Director at Merck Research Laboratories, Vice President of Vaccines Research and Gene Therapy at Chiron Corporation, Senior Advisor in Vaccinology at the Bill and Melinda Gates Foundation, Vice-Chairman of Transgene, and Executive Vice-Chair of the International Vaccine Institute (IVI), an independent international organization with signatory countries in Seoul, Korea established by UNDP.
Dr. Liu consults in the fields of vaccines and immunotherapy for companies, universities, and non-governmental and scientific governmental organizations, and is a Foreign Adjunct Professor at the Karolinska Institutet in Stockholm, and an Adjunct Full Professor at the University of California, San Francisco. She is the immediate Past-President of the International Society for Vaccines.

Dr. Liu’s expertise is in the use of gene-based vectors for the development of preventions and treatments for infectious diseases and cancer, specifically vaccines and immunotherapeutics. Two of the technologies that she pioneered have now been developed by companies into licensed products: bispecific antibodies for cancer therapy, and DNA vaccines (for veterinary applications and which are in numerous human clinical trials for vaccines-for example, the first two Zika vaccine clinical trials), gene therapy, and immunotherapy for cancer, autoimmune diseases, and allergy.

Dr. Liu was invited by the Nobel Committee to lecture in the Karolinska Research Lecture series, was named one of “The 50 Most Important Women in Science” by Discover magazine, and has received a number of honorary lectureships. She has had the conferral of two honorary doctorates, the most recent being Medical Doctor honoris causa from the Karolinska Institutet, Stockholm, Sweden in 2017.