

# Biography of Pioneers in Plant Biotechnology

## From conception to COVID-19: an arduous journey of tribulations of racism and triumphs

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### Summary

Growing up in a densely wooded tropical forest enhanced my curiosity in plants and reading biography of Marie Curie profoundly influenced pursuit of my research career. Early in my career, I developed *in vitro* functional chloroplasts, capable of expressing foreign genes and this laid the foundation for the chloroplast genetic engineering field. Four decades of research has advanced chloroplast bioreactors for production of industrial enzymes or biopharmaceuticals by small or large companies. Because I experienced firsthand horrors of expensive vaccines or medicines, I devoted most of my career to develop affordable therapeutics. During this long journey, I suffered institutional racial discrimination but was rescued by several guardian angels. This biography gives readers a glimpse of tribulations and triumphs of my journey and recognizes important contributions made by my mentees.

### Box 1. Technical Biography1

Henry Daniell is internationally recognized for his work on chloroplast engineering and plant molecular pharming. Henry's pioneering contributions to science have led over the years to the development of several orally deliverable biopharmaceuticals for the treatment of major metabolic and genetic disorders such as Alzheimer's disease, diabetes, hypertension, haemophilia, retinopathy and more recently COVID-19. His work on chloroplasts has also led to the development of promising booster vaccines for the prevention of global infectious diseases like tuberculosis, malaria, cholera and polio. Henry is a Fellow of the American Association for the Advancement of Science since 2007 and the fourteenth American citizen in more than 200 years, to become a member of the Italian National Academy of Science. His contributions to biotechnology have been recognized by prestigious awards from several organizations including the Bill & Melinda Gates Foundation, Bayer Hemophilia Foundation, the American Diabetes Association and the American Heart Association. Henry is the Technology Founder of PhylloZyme, a biotech start-up involved in the production of leaf-based enzymes for textile-, detergent- and food/feed-related applications. He currently is W.D. Miller Professor and Director of Translational Research at the University of Pennsylvania School of Dental Medicine, and Vice Chair for the Department of Basic and Translational Sciences at the same institution. Henry is a Founding Editor, and current Editor-in-Chief, of Wiley's high-ranking *Plant Biotechnology Journal*.

The densely wooded 800-acre Madras Christian College (MCC) campus, India, where I lived most of my early years, sparked my curiosity in plants. Observing the pitcher plant that captured insects, trees that produced fruits in the shape of a human skull, wild orchids, bright wildflowers and dense vegetation amidst monsoon rains was exciting but also scary due to the wildlife, especially foxes and snakes. I was born in Salem, India, located at the foothills of mountains, tenth in a family of twelve, where my father was a high court judge. Sadly, he died when I was 12, and my eldest brother, a professor of English at MCC, became my guardian along with my mother. I majored in botany and thoroughly enjoyed collecting native plants and preparing hundreds of herbarium sheets during B.S. and M.S. studies. After reading a book on Marie Curie, I was inspired by her passion for scientific discovery, and this profoundly influenced pursuit of my own career in research. Declining an offer for a doctoral fellowship in Germany, I joined Madurai Kamaraj University (MKU) for a Ph.D. Program where I fell in love with photosynthesis. After my graduation in 1980, I received a job offer from the University of Illinois, Urbana-Champaign (UIUC), where my doctoral thesis was evaluated. In Prof. Constantin Rebeiz's laboratory at UIUC, I demonstrated efficient chlorophyll biosynthesis *in vitro*, at rates higher than *in vivo* (1980–1982). After completing my postdoctoral training, I returned back to MKU where I developed an *in organello* system that could synthesize a fully functional photosystem I, macro-grana and photosystem II capable of oxygen evolution. I was able to develop chloroplasts capable of prolonged protein synthesis, for up to eight hours (Daniell *et al.*, 1986a). Due to unpredictable power failures during the daytime at MKU, I hitched rides in lorries to the university and performed experiments at night, when the power supply was more stable. During this period, Prof. Bruce McFadden from

Washington State University (WSU) visited MKU as a Fulbright scholar. Intrigued by my passion and determination to advance chloroplast genetic engineering, he offered me a long-term position at WSU. From 1984 to 1990, I enjoyed pursuing my dream of chloroplast genetic engineering research and became a permanent U.S. resident (Figure 1a).

### Pioneering the concept of chloroplast genetic engineering

Because chloroplasts produce RuBisCO, the most abundant protein on Earth, I imagined that these organelles could serve as bioreactors to make other useful proteins. The concept of chloroplast bioengineering dawned on me with the idea of introducing foreign genes into isolated chloroplasts and reintroducing the modified chloroplasts into protoplasts to regenerate 'transplastomic' plants. In the mid-1970s, uptake of green chloroplasts by albino protoplasts and regeneration of green or variegated plants had been widely reported (Bonnett, 1976; Bonnett & Erickson, 1974). From then, I invested my creativity and hard work to establish an efficient and prolonged *in organello* translational system using isolated chloroplasts. At WSU, I used isolated chloroplasts and the cyanobacterium *Anacystis nidulans* to understand the process of DNA uptake (Daniell *et al.*, 1986b; Daniell & McFadden, 1986, 1988). It was gratifying to publish the first studies on the uptake and expression of bacterial and cyanobacterial genes by isolated chloroplasts (Daniell & McFadden, 1987). After reading these publications, Prof. Lawrence Bogorad – then president of the U.S. National Academy of Sciences (NAS) and the American Association for the Advancement of Science (AAAS) – invited me to visit Harvard University on sabbatical leave in 1988. At Cornell University during this period, Prof. John Sanford had designed the Biolistic Particle Delivery System, the so-called gene gun, which we used with my chloroplast vectors to demonstrate the expression of a first foreign gene in chloroplasts (Daniell *et al.*, 1990). Prof. Bogorad communicated this manuscript to the U.S. Proceedings of the National Academy of Sciences (PNAS) while magnanimously declining authorship and then proudly citing this publication among a dozen key articles in his introduction to the Molecular Biology of Plastids book (Bogorad, 1991). Our publications in PNAS resulted in the oldest patents on chloroplast genetic engineering (Daniell and McFadden, 1988) and enabled the creation of a first biotech company, Chlorogen inc., based on the use of chloroplast technologies. After three decades of research, vast majority of transplastomic studies use the *psbA* regulatory sequences that I introduced in our very first chloroplast DNA vector made in 1986 (Daniell *et al.*, 2016a,b).

### Contradicting concepts in chloroplast vector design

Similar to the invention of the gene gun and the creation of chloroplast vectors, an important milestone in the field has been the identification of the *aadA* gene (Goldschmidt-Clermont, 1991), a selectable marker used for the introduction of more than 300 foreign genes into the chloroplast genome. In contrast to the approach of Prof. Pal Maliga at Rutgers University of inserting foreign genes into transcriptionally silent spacer regions of the chloroplast genome large single-copy (LSC) region (Svab

and Maliga, 1993), I hypothesized that insertion in the transcriptionally active spacer regions would utilize the transcription machinery of native chloroplast operons and enhance both the transcription and translation of foreign genes. I could demonstrate the advantages of inserting foreign genes into the inverted repeat region to double the transgene copy number and take advantage of the copy correction mechanism to accelerate homoplasmy (Daniell *et al.*, 1998). The presence of the chloroplast origin of replication within the flanking sequence provided more copies for integration. These and other concepts developed in my research programme, notably related to codon optimization, polycistrons and operons (Kwon *et al.*, 2016), are now used in several laboratories involved in transplastomic research around the globe (Jin & Daniell, 2015; Daniell *et al.*, 2016 a,b).

### Crop chloroplast genomes

Although the tobacco chloroplast genome was sequenced in 1986, for two more decades only five other crop chloroplast genomes were sequenced. Chloroplast regulatory sequences are species specific, and their sequences or binding proteins are not well conserved. Likewise, not even a single intergenic spacer region is conserved among chloroplast genomes in the grass family, and 100% identical spacer regions are required for transgene integration via homologous recombination (Ruhlman *et al.*, 2010). In practice, using heterologous regulatory elements for transgene expression is usually not working, as illustrated for instance by the lettuce *psbA* sequence reducing transgene expression by 80–97% in tobacco, and vice versa for the tobacco sequence in lettuce, when compared to endogenous regulatory elements (Ruhlman *et al.*, 2010). This prompted us to sequence chloroplast genomes from different crops used in everyday life, including soybean, cotton, potato, tomato, grape, citrus, coffee, carrot, cassava, chickpea, cocoa, peach, chestnut, barley, sorghum and turfgrass (Daniell *et al.*, 2016b). This field is still lagging behind because < 70 genera have sequenced chloroplast genomes among >3000 cultivated crops.

### Engineering valuable agronomic traits in the tobacco model system

Conceptual advancement in chloroplast vector design has facilitated the expression of foreign genes in chloroplasts to confer valuable agronomic traits. Stable expression of the *Petunia EPSPS* gene (provided by Monsanto) via the chloroplast genome conferred high-level tolerance to glyphosate when tobacco was sprayed with the commercial herbicide Round-Up. Transgene escape via pollen and the possibility of weedy relatives capturing this valuable trait were major concerns at this time, and therefore, the integration of a herbicide resistance gene in the chloroplast genome and the demonstration of transgene maternal inheritance was considered then a major accomplishment, an invention that was featured on the cover page of Nature Biotechnology (Daniell *et al.*, 1998) and widely debated in several journals and the public press.

Likewise, the development of insect resistance to biopesticides was considered a potential problem due to the low-level expression of truncated *Bacillus thuringiensis* (Bt) endotoxin proteins in GM crops. By comparison, when a full-length *B. thuringiensis* Cry2Aa2 protoxin gene was expressed in

chloroplasts and fed to tobacco budworm, cotton bollworm or beet armyworm, insects with 20,000–40,000-fold resistance to Cry1A or Cry2Aa2 were killed with 100% mortality (Kota *et al.*, 1999). We also introduced the Cry2Aa2 operon into the chloroplast genome, which allowed Bt toxin expression up to 46% of total leaf protein, the highest level of insecticidal protein reported to date in the published literature (DeCosa *et al.*, 2001). Electron micrographs in this publication showed Bt crystals in chloroplasts similar to those naturally observed during sporulation in *B. thuringiensis*. Insects that are difficult to control, including the cotton bollworm and the beet armyworm, were killed after only a single bite of transplastomic leaf tissue expressing the Bt crystals. This paper was featured on the cover of *Nature Biotechnology*, with the caption 'Clear as a crystal'. Few years later, we engineered several operons towards remodelling isoprenoid pathways, terpene and artemisinin biosynthesis. Very high levels of the PHBA polymer, reaching up to 26.5% of leaf dry weight, were obtained through this chloroplast metabolic engineering strategy (Vitanen *et al.*, 2004).

### Engineering crop chloroplast genomes with valuable agronomic traits

Although these were exciting developments, there was great need to demonstrate these concepts in crop plants. However, this was not easy because the regeneration of cereals or legumes following transformation required somatic embryogenesis. We demonstrated the concept of generating transplastomic lines via embryogenesis using non-green carrot cells with the betaine aldehyde dehydrogenase gene inserted into the chloroplast genome. Transplastomic carrot plants grew well in the presence of NaCl concentrations reaching 400 mM, the highest level of salt tolerance reported to date in the published literature (Kumar *et al.*, 2004). Using similar approaches, the Bayer Crop Science group transformed the soybean chloroplast genome to introduce herbicide and insect resistance genes, created marker-free transplastomic lines (Dufourmantel *et al.*, 2005, 2007) and advanced them to field trials. These products were not commercialized because GM soybean using nuclear genetic engineering



**Figure 1** (a) Professor McFadden's laboratory, Washington State University, 1984. (b) Prof. Daniell inducted as the Fellow of the American Association for the Advancement of Science, Boston in 2008. (c) President Gutmann interviewing Prof. Daniell on stage at the Power of Penn event in London, 2018. (d) Prof. Daniell receiving the Pegasus Professorship and University Board of Trustee Chair awards at the University of Central Florida, 2002. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

had already captured the marketplace. Therefore, we focused our efforts on traits that required high levels of expression, unattainable via nuclear genetic engineering.

### Chlorogen, the first chloroplast biotechnology company

Chlorogen Inc. was registered in 1997 in Delaware, USA, when I was a Professor at Auburn University, with Mr. Mike Alder as my business partner, who was advising the governor's office in Alabama on biotechnology. I was invited to present our work at Burrill & Co. in April 2002, at the top floor of the Embarcadero Center in San Francisco, CA, overlooking the San Francisco Bay. Although I was told that Burrill had seen lots of protein production platforms, I was thrilled to receive a second invitation for further discussions over an entire day. Dr. Roger Wyse at Burrill, formerly the Head of the Agriculture Division at Rutgers University, decided to establish Burrill & Co. as the lead investor in Chlorogen with three more partners as co-investors. One of the co-investors, Prolog Ventures, was located in Missouri and required Chlorogen to be located near Monsanto. Ironically, Monsanto closed down its research on chloroplast genetic engineering the week Chlorogen started functioning in their incubator facility. Chlorogen received The Frost & Sullivan Entrepreneurial Award for identifying a unique and revolutionary product solution with significant market potential. Chlorogen's business team negotiated licensing deals with DuPont, Dow Agro Sciences and Sigma Aldrich. Unfortunately, the University of Central Florida withdrew the licence from Chlorogen in 2007 because it did not meet the key milestone of developing a product.

### Enzyme products made in leaves launched by PhylloZyme

Learning valuable lessons from the failure of Chlorogen and unwilling to give up, I persuaded investors of the biotechnology start-up PhylloZyme – who also have ownership in the textile and microbial-enzyme business – to develop products that required minimal regulatory approval. Most current genetically modified plant commercial products on the market are derived from seeds, and therefore, it was quite thrilling to launch a first leaf-made protein product for commercial use developed by PhylloZyme in the summer of 2018 (Daniell *et al.*, 2019c; Kumari *et al.*, 2019). Dry leaf-pectinases were validated with eight liquid commercial microbial-enzyme products for textile or juice industry applications. In contrast to commercial liquid enzymes requiring cold-storage and transportation, leaf-pectinase powder could be stored up to 16 months at ambient temperature, without need for any protective formulation or loss of enzyme activity. Natural cotton fibre does not absorb water due to the hydrophobic nature of waxes and pectins. After bioscouring with pectinase, they readily absorbed water in a few milliseconds, meeting industry requirements.

Similarly, four newly launched leaf-enzyme products (endoglucanase, exoglucanase, lipase, mannanase) were also compared and validated with 15 commercial microbial-enzyme products for the detergent and textile industries (Kumari *et al.*, 2019). Leaf-lipase/mannanase crude extracts removed chocolate or mustard oil stains effectively at both low and high temperatures. Endoglucanase and exoglucanase in crude leaf extracts removed dye efficiently from denim surfaces and depilled knitted fabric by

removal of horizontal fibre strands. Thus, the PhylloZyme leaf-production platform offers a novel low-cost approach by the elimination of fermentation, purification, concentration, formulation and cold-chain storage/transportation. This is the first report of commercially launched protein products made in leaves and validated with current commercial products.

### Advancing protein drugs made in chloroplasts to the clinic

While non-therapeutic proteins/enzymes are advanced quickly to the market, the timeline for advancing therapeutic products are much longer. The first vaccine antigen (CTB) was expressed in chloroplasts two decades ago (Daniell *et al.*, 2001), followed by several other vaccine antigens to treat malaria, tuberculosis, HIV, dengue, anthrax plague etc., and their efficacy have been evaluated using pathogen or toxin challenges (Chan & Daniell, 2015). More recently, vaccine antigens against infectious diseases have been evaluated by the FDA and CDC, supported by the Gates Foundation. Oral delivery of chloroplast-made polio viral protein 1 (VP1) antigen common to all polio serotypes conferred both mucosal and systemic immunity, generating both IgA and IgG1 antibodies specific to VP1. Poliovirus neutralization studies performed at the CDC, using hundreds of sera samples from my laboratory, showed seropositivity against all three poliovirus serotypes (Chan *et al.*, 2016; Daniell *et al.*, 2019b). This offers a timely solution for developing countries that could afford only a single dose of IPV when OPV 2 was withdrawn by WHO, because it could revert to virulence by point mutations or recombination with other enteroviruses.

The SARS-CoV-2 virus responsible for coronavirus disease 2019 [COVID-19] infects human respiratory cells via binding to the angiotensin-converting enzyme 2 [ACE2] receptor and is easily transmitted. There are >50 vaccine clinical trials in progress that will primarily produce systemic but not mucosal surface immunity that is required to protect at the surface of viral entry. In addition, waning of antibody response (as seen already in repeat COVID-19 infection) or poor immune response in elderly patients would require multiple boosters and scale up capacity to vaccinate the global population. Therefore, my laboratory is now developing oral booster vaccine to facilitate long-term mucosal immunity in elderly patients, provide protection against reinfection and for affordable mass vaccination, to deal with COVID-19 pandemic that has devastated global health and economy.

Over the last fifty years, injections of recombinant human insulin made in yeast or bacteria saved millions of lives, but these products are not affordable for more than 90% of the global diabetic population. Insulin pumps cost \$6,000-12,000 while one-third of the global population earn less than \$2 a day. Therefore, several human therapeutic proteins have been expressed in chloroplasts to develop affordable protein drugs to treat diabetes, hypertension, heart failure, retinopathy, haemophilia or Alzheimer's disease (Daniell *et al.*, 2016a, 2019a). Protein drugs can be produced in lettuce chloroplasts in cGMP facility and they are stable in lyophilized plant cells for several years when stored at ambient temperature, eliminating the cold chain for storage and transportation (Su *et al.*, 2015). The plant cell wall efficiently protects vaccine antigens from digestive enzymes and acidic pH, and gut microbes digest plant cell walls to release antigens in the gut lumen. Recent advances include expression of human blood proteins after codon optimization (Kwon *et al.*, 2016, 2018) in marker-free lettuce plants, stability of expression

in the absence of antibiotic resistance genes and functional efficacy in animal disease models (Daniell *et al*, 2020; Park *et al*, 2020). In addition to raising the profile of plant biology in the medical field by featuring plant research on covers of medical journals or on featured editorials, these projects received funding from Bayer, Novo Nordisk, Shire, Takeda and NIH SMARTT program to produce clinical grade materials, conduct third party toxicology/pharmacokinetic/regulatory studies at Stanford Research Institute and results of these studies have been published recently (Daniell *et al*, 2020; Herzog *et al*, 2017).

The SARS-CoV-2 spike protein binds to ACE2 with high affinity, infects alveolar cells, results in lung injury and dramatically lowers ACE2 levels. In healthy human lungs, ACE2 produces surfactants to protect alveoli from collapsing and cytoprotective anti-inflammatory Ang (1-7) peptide. Thus, ACE2 supplementation is beneficial by serving as a decoy to reduce SARS-CoV-2 entry into human cells and by protecting against lung injury via the anti-inflammatory actions of Ang (1-7). My laboratory has produced clinical grade oral ACE2. Oral delivery results in 10-fold higher

concentration in lungs and prevents and treats pulmonary hypertension at doses with no evidence of toxicity (Daniell *et al*, 2020). Therapeutic efficacy and safety of supplementing ACE2 and Ang (1-7) with this existing product in non-critically ill COVID-19 patients in the hospital and at home is in progress. By employing an integrated Phase 1 and Phase 2 clinical trial design, this clinical trial addresses an urgent unmet medical need to treat the growing population of COVID-19 patients and protect them from lung and extra-pulmonary tissue injury.

### Expression of deep gratitude to my guardian angels

As a plant biologist, I consider myself extremely fortunate to be teaching at an Ivy League University, featured among the most eminent scholars of this institution by President Amy Gutmann at the Power of Penn, London (Figure 1c), and being a recipient of the W.D. Miller Professorship. Launching of the first products using this new platform technology developed in recent years



**Figure 2** (a) Prof Daniell delivering convocation address at the University of Central Florida, 2004. (b) President Kalam posing with B-glucosidase-expressing plants with increased height and biomass, created by Dr. Shuangxia Jin, 2009. (c) Prof Daniell receiving the American Heart Association award, Washington DC, 2015. (d) Prof Daniell receiving American Diabetes Association award, 2008. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

would not have been possible without the help of the Pennovation Center and without the University of Pennsylvania's administration bold decision of building a high-tech, Nature/BBC-featured greenhouse facility. I am grateful to Professor Charles Arntzen for nominating me as a Fellow of the American Association for the Advancement of Science in 2007 for my efforts in advancing the concept of expressing vaccines and other biopharmaceuticals in chloroplasts (Figure 1b). As pointed out earlier, I am grateful to Prof. Laurence Bogorad for inviting me on sabbatical, paying for the Harvard Radcliff guest house, communicating my manuscript to PNAS and declining authorship in order to promote a foreign young scientist to lead this field. Dr. Andrew Marshall, Editor-in-Chief of *Nature Biotechnology*, believed in this concept when it was shunned by many in this field, featuring chloroplasts several times on the journal's cover and ranking my research among the top ten inventions of the decade in 2007. Likewise, I am grateful to biomedical journals such as *Blood*, *Hypertension* and *Molecular Therapy* for not only publishing our plant biology articles, but also writing featured editorials, highlighting our work on the cover or granting us 'best paper' awards.

I was also honoured by my induction into the Italian National Academy of Sciences in 2004, which is highly recognized at the

University of Pennsylvania because its founder, Benjamin Franklin, was the first American to receive this honour in 1786. I have been the 14<sup>th</sup> American in 218 years to receive this honour, and I have truly no clue of how I was nominated for this recognition! The award ceremony to receive this honour was in Italian, and the only words I could understand were chloroplast and, of course, my name. . . Indeed, the award invitation letter was mis-mailed to a bank in Orlando, Florida. When I finally received the letter with several redirected addresses on the envelope, I discarded it unopened. Fortunately, my wife Shobana, picked up the letter, advising me never to trash letters without opening them! I will be eternally grateful to Prof. Keith Edwards for inviting me to be a founding Associate Editor of the *Plant Biotechnology Journal* (PBJ) in 2002 and passing on the baton to be the Editor-in-Chief in 2012, and continued support by Prof. Paul Hutchinson and Martin Parry. I am delighted that PBJ is now consistently ranked among the top few plant science journals publishing original research and offers readers free global access.

Likewise, the success of the book on *Molecular Biology and Biotechnology of Plant Organelles* (Springer 2003), edited by Dr. Christine Chase and myself with the contributions of 44 international authors, was immensely satisfying to me and educational to new investigators. Along with Dr. Jihong-Liu



**Figure 3** (a) Prof Bogorad visiting the Daniell laboratory at Auburn University, 1995. Sam Verma and Madhuri Kota created & characterized transplastomic plants expressing Bt crystals. (b) Prof Daniell laboratory at Auburn University includes pioneering contributors Drs. Lee and Guda who made chloroplast vectors and created first transplastomic plants with herbicide resistance or producing biopolymers. (c) Prof Daniell laboratory at the University of Central Florida visited by Prof. Maliga. Dr. Samson Nalappalli standing at the back created the first lettuce transplastomic lines; several products made in lettuce chloroplasts are now advanced to the clinic. (d) Daniell laboratory greenhouse at the University of Pennsylvania was featured in *Nature* 2015, BBC and includes Dr. Jin Su who produced first commercial scale lettuce expressing blood clotting factor IX and Dr. Kwang-Chul Kwon who produced angiotensin-converting enzyme and clotting factor FVIII that are advanced to the clinic for treatment of Covid-19 or hemophilia. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Clarke, I also had the opportunity of organizing the first conference on chloroplast biotechnology in 2006, that was attended by more than 300 participants from 20 countries worldwide. It was amazing to see this new field of research pioneered in my laboratory pursued by so many investigators worldwide and gratifying to see the output of this first conference giving rise to a new, and still continuing, Gordon Research Conferences series on chloroplast biotechnology.

I was the recipient of the highly coveted campus-wide Sigma Xi Award (Auburn University) and Pegasus Professorship, Board of Trustees Chair for best teaching, research and service (Figure 1d) and addressing the commencement ceremony (Figure 2a), a rare honour conferred to a faculty member. Other high-points of my career included presentations to U.S. Senate committees; visits to my laboratory by the President of India (Figure 2b), U.S. Governors and Senators; receiving the top global Bayer haemophilia research award in Buenos Aires and awards from the American Heart Association (Figure 2c) and American Diabetes Association (Figure 2d); serving as a United Nations Consultant in Biotechnology; and being recognized in public media including the BBC, CNN, VOA, Discovery Channel and other global newspapers.

### Firsthand experience of American institutional racial bias

Early in my career, I endured lots of discrimination. I was routinely mistaken as the mailman for Dr. Daniell when I carried my proposals or documents for signatures. Grant reviews frequently questioned my educational background abroad. Institutional bias was evident when NSF plant genome repeatedly refused to fund projects on the sequencing of crop chloroplast genomes that were ultimately funded by a line-item in the U.S. Congress, a stunning example of discrimination by peers and need for transparency in the NSF review process. At the University of Idaho, I was denied tenure even with several publications in P.N.A.S., grants from federal and state agencies and an invitation from Prof Bogorad, the president of the US National Academy. Thankfully, this challenge was quickly resolved by guardian angels like Prof. Brent Nielson, a former collaborator, and Prof. Joe Cherry who offered me a tenure track job leading to a full professorship at Auburn University. I will never forget Prof. Cherry surprising me, at the end of a faculty meeting, with a huge cake decorated with the American flag, when I became a U.S. citizen in 1993. In sharp contrast to numerous examples of successful Indian Americans in all walks of life and scientific careers, it is unfortunate that not a single Indian man has been recognized as a N.A.S. member in the Plant Biology section since 1863 or rare to see such awardees in the American Society of Plant Biology, established in 1920s. Such examples would indeed encourage hundreds of scientists to pursue their careers in plant biology, and for this reason, I am raising awareness of racial inequalities among foreign-born plant scientists in the United States. Finally, scientific journals are acknowledging racial discrimination rampant for decades (Cell Editorial, 2020).

### Epilogue

After many years of experience in science, my greatest satisfaction is to see many of my mentees lead multi-disciplinary research programmes in medical schools, industry, academia or federal agencies, including the West Wing of the White House as Presidential Innovation Fellows. I am proud to share photographs

of my laboratory colleagues at Auburn, University of Central Florida and Pennsylvania (Figure 3a–d), who made significant contributions to advance this field. My prayer for my mentees is not to get discouraged by institutional racial bias or discrimination but to believe in the power of persistence over prejudice. In my life, American institutional bias was compensated by European institutions and noble Americans. Most importantly, passion for one's career and commitment will overcome adversities. My passion for chloroplasts has lasted for four decades, and I can't stop thinking about new opportunities for chloroplast genetic engineering. When I grew up in India, I experienced firsthand the horrors of people dying without access to medicines or vaccines. Therefore, I am deeply committed to advancing my inventions to the clinic and to make affordable protein pharmaceuticals for the global population. I am thankful to my research team members for their hard work, and to my wife Shobana and my sons, Luke and Paul, who made great sacrifices to help me realize this goal.

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