Visions of the Future

Two Cancer Researchers Share Their Stories

by Deborah C. Coffin

UNIVERSITY OF NEBRASKA'S MEDICAL CENTER

David Wilson works with students nominated to participate in the Science Education Partnership Award in Nebraska.

Two young scientists from very different corners of the country have hurdles many would consider impassable. David Wilson, Navajo, sold his house and cars, and with his wife and newborn in tow, moved in with family so that he could attend graduate school in a field where, as a Native American, he would be a pioneer. Dana-Lynn Koomoa, Native Hawaiian, participated in competitive judo which prolonged her undergraduate degree over many long years. She attended three different schools and held down various jobs to reach her dream. These young researchers have also, remarkably, found the time to reach out to others through their extensive mentoring efforts.

The two were brought together recently as Fellows of Keystone Symposia (see sidebar), a research-driven, diversity-centered program designed to educate early career scientists regarding the inner workings of the life sciences community. *Winds of Change* had the opportunity to speak with them about their career choices.

David Wilson

David Wilson, Navajo, a scientist at the National Institute on Aging, a division within the National Institutes of Health (NIH), conducts fundamental research into a protein called SIRT6 that seems to be a key player in determining life span. Mice bred to have an absence of SIRT6 will die from a fatal drop in blood sugar, or hypoglycemia. A recent research study at Massachusetts General Hospital's Cancer Center found that "SIRT6 functions as a master regulator of glucose levels by maintaining the normal processes by which cells convert glucose into energy," explains Raul Mostoslavsky, MD, PhD, who led the study. "Learning more about how this protein controls the way cells handle glucose could lead to new approaches to treating Type 2 diabetes and even cancer."

Winds of Change (WOC): *Could you explain to me the function, as it's currently known, of the SIRT6 protein?*

Wilson: The proper name is actually Sirtuin 6. They just call it SIRT6 or SIRT6 for short. Since I'm at the National Institute on Aging, we study the role of SIRT6 on longevity—how the function of this enzyme contributes to the longevity of an organism. It's been shown that if you over-express this particular enzyme in yeast, worms, flies...a number of different animals, including mice cells, that you actually increase their life span. We're analyzing the function of this enzyme to see if we can determine what it is actually doing. So far, what we've been able to discover is it's a specific H3G9 histone deacetylase. That means it has a negative function on gene activity. So it's able to shut down certain genes. And in the absence of SIRT6, certain genes are up-regulated or expressed at a higher level and this can cause problems within an animal or in cells.

WOC: *What happens when it's over-expressed?*

Wilson: When it's over-expressed, it actually suppresses the aging phenotype. When it's "knocked out" of the organism, when there's a loss of SIRT6, you actually negatively regulate certain gene subsets. And those genes are what cause advanced aging or the progeria phenotypes.

WOC: *What happens when the SIRT6 protein is "knocked out" in terms of blood sugar specifically?*

Wilson: A recent paper published in *Cell* by Raul Mostoslavsky's group showed that when the SIRT6 gene was knocked out in mouse models, it triggered a severe metabolic phenotype. Loss of SIRT6 triggered a nutrient stress response that caused cells to switch from glucose metabolism toward glycolysis, ultimately resulting in lethal hypoglycemia. Hypoglycemia, or low blood sugar, is also a common feature of diabetes. When you knock out the SIRT6 in mice, they're a lot smaller, they have a lack of subcutaneous fat, and severe glucose imbalance.

We've chosen an emerging model system, DT40 Chicken B cell lines that we can easily manipulate the genome by knocking in or knocking out genes of interest. We're using chickens because they're an easily manipulated cell line. We don't right now have access to the mice because they're in a competitor's lab. We have created an SIRT6 knock out cell line and completed several genome-wide studies to establish a comprehensive list of genes controlled by SIRT6 in mammalian cells.

WOC: *Can you talk about your upbringing?*

Wilson: I was born in Columbus, Ohio, because my dad was a military man and he was stationed in Ohio. However, I was raised in New Mexico. I was six months old when we moved

Keystone Symposia

Keystone Symposia on Molecular and Cellular Biology organizes conferences to connect the scientific community and accelerate discoveries to benefit the world community. Included in its mission is support for early-career scientists including those who represent federally designated underrepresented minority populations. General scholarships as well as scholarships specifically designated for underrepresented ethnic minorities in the sciences are available for attending Keystone Symposia conferences.

For more information, visit www.keystonesymposia.org

to Manuelita, New Mexico. I grew up in a little town...well, they call it a town...but it was four houses. It constituted this little area, 18 miles west of Gallup, New Mexico, just off of old Route 66. It was part of the Navajo Nation Reservation. Another 18 miles north is the capital of the reservation, Window Rock, Arizona. It's very close to the Four Corners area.

WOC: *How, coming from a tiny town with only four houses, did you become interested in science?*

Wilson: I went to high school in Gallup, New Mexico. Which is quite far—we had to be bussed in. I actually excelled. So I graduated from high school with a full ride to the University of Arizona. The area where we lived in is a heavy mining area where the Pittsburgh and Midway Company used to be. They mine coal. And that's what my stepfather did. So the family felt I should become an engineer and continue to work in the area. So I went to the University of Arizona under the impression that I was going to be a mechanical engineer. I went through two years of schooling and I absolutely hated it. Then during the summer, on break, a kid walked up to me and handed me a flyer. It said, "Go on a very nice summer vacation for free." I looked at it and thought, "Cool." It was an opportunity to do basic research at the Rocky Mountain Biological Laboratories in Gothic, Colorado. I thought, "Why not? I'm here and hating it here…" So I ended up chasing butterflies for the summer in Colorado; I think it was a six-week program. This experience changed my entire outlook on what I wanted to do for the rest of my life. We were studying a native butterfly called Goloptus psychlictuimus. It's a silvery blue butterfly. We were looking at why the female lays her eggs on specific plant calyxes. Come to find out, the calyxes they were laying on are toxic to cows. So the cows would not eat them and their offspring would survive. This is the whole thing that got me going. Before I'd even finished the summer program, I filled out the paperwork to change my major. I moved from Tucson and went north to Tempe, Arizona. That's when I began my tenure at Arizona State. I took up a major in molecular and cellular biology.

Because of the transfer, I lost my full scholarship. But I'd found what I knew I wanted to do for the rest of my life. Nobody I had ever known had a degree in molecular biology. So I didn't know what I would do with this degree or if it was worth anything. I was apprehensive about that but I did receive financial aid. Most of the people I know, who come from a similar background and have limited family support, receive aid. When I first got there, most of my credits transferred, so during the first two years I started working at a private company. It was an environmental laboratory. We tested water samples, we tested food for nutritional labeling, and food for food-poisoning screens. This is where I really began to develop my science skills. We tested water and soil samples for chemical contaminants. This was all under FDA and EPA guidelines so it was a very strict, stringent controlled laboratory setting.

David Wilson holding a tube of a recombinant SIRT6 peptide

I think the two gentlemen who decided to give me a shot at it probably did so because I was willing to work for almost nothing. It was a start-up lab so they weren't sure how far this was going to go. I held several different titles. I became the director of chemistry and I became the director of microbiology, and then I became the director of research and development later on down the line.

I graduated after two years. After graduation, I moved into a full-time position. During that time, I made enough money to buy a house. So I bought a house on a corner lot—it was a beautiful house. I had two cars in the garage and my wife and I sat down one day and said this is not what we want to do for the rest of our lives. I wasn't happy with what I was doing. It had become routine. I was doing the same things every day. So we made the conscious decision that for us to move forward, I needed to get my PhD. In order for that to happen, we had to sell the house. We had to sell the cars and we had to move back in with her mother, who lived in Phoenix, to have the financial means to go back to school. It was a huge sacrifice. It's something I will always cherish my wife for. She knew my potential and she stood beside me 100%. She was willing to go through all of that with me.

WOC: *At this point you had a vision. How many schools did you apply to?*

Wilson: One school. I was setting a precedent in my family. I was the first go to college, the first person to graduate from college. I was the first person to go to graduate school and get an advanced degree. So I had no idea how to embark on the process. The decision to go to the University of Arizona was because of my family. I probably could have gone to other places if my family ties hadn't been there. We had a newborn and my wife had her job there. And her family was there in Phoenix as well.

It's paid off. I got through the graduate program.

WOC: *And how did you end up at NIH?*

Wilson: [The project I am currently working on] is not actually the project that lured me to the NIH. The project that lured me, that I have a very strong interest in, is the evolution of the immune system. Throughout my graduate career at Arizona State University, I worked with a certain set of enzymes called RAG enzyme, RAG 1 and 2. They're involved in immunoglobulin or antibody diversification. While studying these enzymes, one of the leaders at that time was Sebastian Fugmann. He was a post-doc in David Schatz's lab at Yale and they were doing really nice work. I had met him once at a meeting, a national science meeting. Then in the latter stages of the program, I was keeping tabs on Fugmann's work and where he was and I decided this was the guy who I wanted to teach me what I needed to learn to become a successful independent researcher.

The NIH doesn't cover your moving costs. So we packed up everything, dumped out our entire savings, rented a U-Haul and drove for three days to

the East Coast. [I had only been there] for conferences lasting one or two days. But never for a long period of time. It was a huge adjustment for all of us.

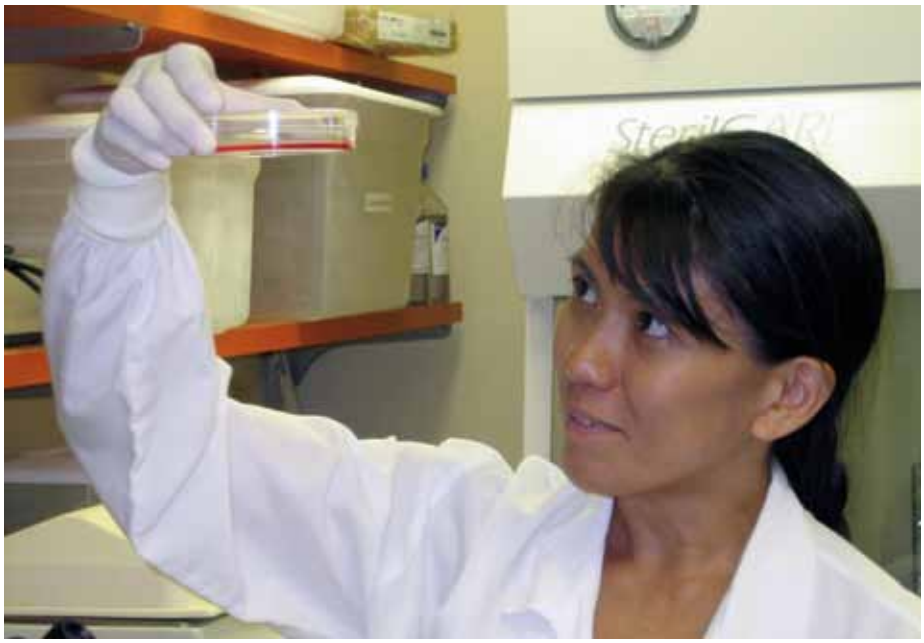
WOC: *Can you discuss ways in which young Native people can overcome their apprehension about higher education?*

Wilson: Through all of my explorations, adventures in outreach and from personal experience, I recognize that what many Naive Americans need to overcome is a confidence issue. I've done so many outreach trips to the Southwest, to give keynote talks at the University of New Mexico and other areas. I've found so many talented young Native Americans, diamonds in the rough. They're hiding out in the Southwest and it's our job to go out there and find them. I recently recruited a young lady from Las Cruces, New Mexico, from New Mexico State, Alfreda Nelson. She was very good in the academic setting, getting ready to graduate, but with no idea what she wanted to do for the next step. On one of my sponsored trips, I was put in touch with her. I pleaded with her to come to the NIH for the summer program, where we work to recruit Native American students or other underrepresented minority students to come work under our direct supervision. She fought [this opportunity]. She was very uncertain. She'd never been away from home. Eventually, she committed to the NIH and came here and did research. She was one of the best summer students we've ever had here at the NIA. When she completed her tenure here, she was accepted into the Mayo Clinic for graduate school.

WOC: *What other outreach work do you do?*

Wilson: When I first started here [at NIH], I was invited to participate in a DNA Day event. They bring in kids from the surrounding areas and introduce them to DNA. I was invited to go to the University of Nebraska to help them do their DNA project. They were bringing in kids from the surrounding reservation tribes in South Dakota and Nebraska. The director, Maurice Godfrey, thought it would be a good idea to have role model posters because the kids never come into contact with Native American professionals they can relate to. This was a great idea. For the role model posters, we've been able to recruit an astronaut, me, and many other professionals. All kinds of professionals who are doing very good things out in the work force. This idea is to show kids that it doesn't matter what you do in life, you can become whatever you set yourself out to do.

I want to stress how important it is to promote Native Americans and get them encouraged in the sciences—the earlier the better. That's one of the things we've noticed at the University of Nebraska. We had a batch of middle-school students last year and the youngest were the most engaged and the most interactive in all of our program settings. The high-school students were sitting back to see how the others were reacting to what we were doing.



CANCER RESEARCH CENTER OF HAWAII

Dana Koomoa conducts research that focuses on neuroblastoma

WOC: *What has been the hardest thing you've had to overcome?*

Wilson: Financial hardship. That was one of our most difficult sticking points. It's still difficult to live out here on the East Coast. A lot of people I know don't have the family support because—it's just where we come from. It's up to us to build for this generation so my kids won't have to experience the same thing. Going through school on school loans, it's ugly on the other end of it. Some people are fortunate enough to have their school pay for them, but I wasn't one of them.

On a positive note, I truly believe it only takes one person in someone's life to have a positive impact on them for the rest of their life. My special person was a microbiology professor named Dr. William Burke. Without his guidance, I would not have completed my graduate studies. He constantly gave me pep talks and boosted my confidence. I hope to become somebody who Native American students from around the country will come to if they need advice or somebody to help them. I'd like to be a Dr. Burke. Even if it's just by giving someone a vote of confidence if they have uncertainty in their lives. I've experienced a lot of it and I have a goal to help these kids maneuver past or steer around the potholes that I fell into. That way they could get to where they want to be much faster.

Dana-Lynn Koomoa

Dana-Lynn Koomoa, a Native Hawaiian and post-doc working at the Cancer Research Center of Hawaii in Honolulu, conducts research in three areas focused on neuroblastoma, the most dreaded cancer which occurs exclusively in infants and children. Although neuroblastoma is commonly described as brain cancer, it is not really a brain tumor. It can spread to the brain, but the tumor originates most

often in the nerve tissue of the adrenal glands, abdomen, and along the sympathetic nervous system. Her research areas include elucidating the role of polyamines in the malignant progression of neuroblastoma; working with syrbactins, a new proteasome inhibitor class for cancer treatment; and determining whether PRAF2 may be a prognostic indicator of cancers, specifically neuroblastoma and glioblatoma, as well as a molecular target for therapeutic treatment. Her significant contributions to the research conducted by her supervisor Dr. André Bachmann, an associate professor at the University of Hawaii, may have far-reaching implications for treating and diagnosing other cancers as well.

WOC: *At what age did you become interested in science, or realize that you had talent?*

Koomoa: It was grade school. Everybody who has ever known me since growing up, they've all mentioned that I have always loved animals. I think that's how it started. Because my dad is Hawaiian, we were always at the ocean, with the tide pools. He was always showing us the different organisms and how the waves form, the ecology. That's how I became interested in science.

I grew up on Oahu. We spent a lot of time on the north shore and the west shore—it's less populated and there are a lot of beaches and reefs and tide pools. So with my father, I pretty much grew up at the beach. My dad was really a fisherman at heart, I think. Then he married my mom and wanted to do something more stable. He wasn't a scientist.

The high school I was supposed to go to was in a really bad area. It's a really bad school. I asked my mom to allow me to go to another school that was known to have a really good science and math program. So I was able to go to another district. I knew I wanted to do science and math and I preferred to go to that other high school from which I graduated.

WOC: *Did you participate in any summer programs during high school?*

Koomoa: We had these zoology programs that I was involved in. You would take a course and there were after-school activities that we would do. During the summers, I competed in judo.

Judo really helped me as far as my discipline in school, especially in college [in San Diego, California]. I think I was able to focus a lot better. I was working one or two jobs to support myself through my undergraduate years. And I also did judo. I was still able to manage my time fairly well.

There were not any programs in place in San Diego that were helpful. I felt lost, actually, for awhile. It was really hard to support myself when I was there and I was doing judo at the same time. So I ended up going to community college first. I went to Mesa College and Grossmont. In the beginning, I could take courses that allowed me the flexibility to continue my working and training and going to school. Then I transferred to San Diego State University.

It was really hard to finish my undergraduate degree. Some semesters I was competing all over Europe for a good three or four months, I'd miss a whole semester. So I was juggling my work schedule and everything. I think it was about five years before I even transferred to San Diego State.

WOC: *Your CV shows that you had two senior projects: "Expression of snRNAs [ed.: small nuclear RNAs] during the development of drosphilia larvae" and "Effects of ppTRH on the expression of stress proteins and prolactin release from anterior pituitary." Was that typical?*

Dana-Lynn Koomoa

Koomoa: No. Usually you choose one. Most people would choose one and just do that for the last two years, or at least the senior year. The drosophila project was more interesting because of the biochemistry. I really enjoyed my biochemistry courses and my labs. I really wanted that experience. But I originally got into the other lab, the stress proteins, first. [In that project] we were working with animal models. We did some small animal surgery, so we could inject different compounds. But most of the biochemical work was actually outsourced to other labs. It was the drosophila project with the molecular and biochemical techniques rather than the behavioral aspects [of the stress proteins project] that I preferred.

WOC: *How many schools did you apply to for your PhD?*

Koomoa: I applied to three places and ended up at Brown University. I had moved to Rhode Island because I really wanted to go to Brown. I started working in a volunteer capacity as a post doc with a professor at the University of Rhode Island. He was a microbiologist. I wanted to get more experience in the different techniques. I was still applying to schools and getting used to the area. I worked at Roger Williams Hospital. The professor who ran that hospital was from Brown University. He was testing at a pharmacology lab. They were testing out different drugs,

The Cancer Research Center of Hawaii

The Cancer Research Center of Hawaii, located in Honolulu, is one of only 65 National Cancer Institute-designated cancer centers throughout the United States. As a research unit of the University of Hawaii at Manoa, it conducts cancer research, educational activities, and community outreach. Its research programs focus on the possible causes of cancer and possible reasons for different cancer rates among Hawaii's ethnic groups; reducing the incidence and impact of cancer in the Hawaiian population; and discovering new agents from local plants and marine organisms.

For more information, visit www.crch.org

compounds, things like that.

At Brown they had a great structured program, but they allowed more flexibility in terms of developing a project, the graduate project. Plus, I was teaching, which I really enjoy.

My dissertation subject was the skate and we also worked on the dogfish, a small shark. They have this really sensitive osmo-regulation. As far as changing salinity in the waters when they are migrating, within their red blood cells. So we were studying the mechanisms that these fish have that allow them to traverse through waters that have really vast differences in salinity, the osmolarity of the water. I liked the physiology of it.

My mom got sick during the last part of my PhD so I moved back to Hawaii and started to look for a post-doc here. I worked in the ion channel field for awhile, which was not that different. I went from transporters to ion channels, which I'd actually studied in my graduate work as well, it just wasn't a main part of my PhD work.

The best way to describe ion channels is that cells have a membrane that separate the intracellular components from the outside environment. Ion channels are proteins that create an opening in the membrane to allow passage of ions between the inside and outside environments. There are a variety of ways that ion channels are regulated. Basically, they are pores in the membranes that govern the passage of an ion or ions into or out of the cell based on the size and charge of the ion itself and the electrochemical gradient across the cell membrane. I really wanted to work on a project that was more physiologically and medically relevant, and that's what led me to cancer research.

WOC: *In the abstract from a recent paper you co-authored as a member of the Bachmann group, it mentions that the PRAF-2 protein can serve as a tool for prognosis of not only neuroblastoma and likely other forms of cancer, but that it also might function as a candidate molecular target for therapeutic intervention.*

Koomoa: This PRAF-2 project is not my main project. PRAF-2 is a protein that my supervisor, Dr. Bachmann, discovered when he was doing his post-doc. It hasn't really been clear what the function of this protein is, but as I mention in the abstract, there are two other proteins that are a part of this family: PRAF-1 and PRAF-3. They have been better characterized in different cells.

A couple of years ago, we found that PRAF-2 played a role in neuroblastoma. The expression of this particular protein correlates with unfavorable genetic and clinical features of neuroblastoma. So we started looking at it in glioblastoma, analyzing the RNA levels and its expression in different types of cell lines based on how invasive they were. We also looked at the cell localization of the protein, trying to figure out its function, or to better characterize it in this particular cancer. We also ended up using a cell line to "knock down" the PRAF-2 protein. This means to decrease the expression of that protein in that cell. That allowed us to investigate how PRAF-2 affects different aspects of the progression of this cancer, in terms of growth, proliferation, and invasiveness. This protein exists in normal cells as well. Our hypothesis is that it might play a different role when

it's functioning in cancers as opposed to its function in normal cells.

WOC: *If you were to look at a normal cell you would find it and if you look at these cancer cells you find it as well?*

Koomoa: The expression level changes. It could be higher expression in some cancer cells. That's what we've found in neuroblastoma tumors. We don't know exactly how that expression is regulated in the cells. This project is very much in the beginning phases. We can find the protein by looking at a cancer cell because we have antibodies that we can use to do confocal microscopy. We do fluorescent staining and then see where that fluorescence is localized.

WOC: *So you theorize knocking it down will prevent the cell's abilities to divide?*

Koomoa: We haven't gotten to that animal work with this particular project yet. We're still doing in vitro work. Actually, the animal work and the clinical study that we're involved with is part of another project that I'm involved with, the polyamine project. Most of my papers at the cancer center so far have been on the polyamine project and neuroblastoma. That project is much more established and that's why my supervisor has been able to advance it to clinical trials.

We're starting to continue the in vivo mouse model here to investigate some combination treatments that we're testing. In conjunction with five children's hospitals around the country, Bachmann has put together a neuroblastoma trial that just started. I think they have three patients undergoing treatment.

WOC: *I see on your CV that you work with kids also?*

Koomoa: Yes, I work for a Native Hawaiian education program, Imi Na'auao. I've always been involved with things like that. As an undergrad, I was working with a minority education program in San Diego for elementary school kids. I was teaching biology and chemistry at the time. It was an afternoon program. In San Diego, I worked with the Alana program for incoming freshman students. And then in Hawaii, I started working with the Pacific American Foundation—we're trying to introduce middle-school children to STEM careers.

WOC: *What would you like to see in the next five years?*

Koomoa: I would like to stay in academia and get a professorship here in Hawaii. I would like to see, especially in the sciences, more programs like the ones we've started, but geared toward the transition between high school and college and throughout college for minority students in Hawaii. Based on what I saw while I was on the mainland, there are now more and better programs available there. I would like to see more of that here. ✜

Deborah Coffin is a freelance writer who lives in Berkeley, California.