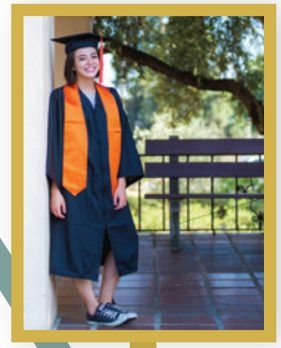
Crossing paths

The two most recent Nobel Prize-winning Caltech alumni talk with a fellow alum about their work, their campus experiences, and life after Caltech.

by Lori Dajose (BS ’15)



Left: **Andrea Ghez** (PhD ’92) in 1987, her first year of graduate school at Caltech. Upper left: **Charles Rice** (PhD ’81), in a photo from the mid–’80s. Above: **Lori Dajose** (BS ’15) at her Caltech commencement.

When you discover someone who has shared with you the Caltech student experience, there is a kind of instant camaraderie. Whether you studied biology in 1980 or planetary science in 2010, you likely can bond over sleepless nights working on hard questions, sunny campus days, and, perhaps most importantly, bright and inspiring collaborators and mentors. In this way, no matter what our life trajectories have looked like, all Caltech alumni have crossed paths.

Though the number of Caltech alumni is small compared to many universities, 24 scientists within our ranks have been recipients of a total of 25 Nobel Prizes; as a whole, 44 Caltech faculty, alumni, and postdocs have won a total of 45 Nobels. Two of those 24 alumni Nobelists joined this distinguished list in 2020: virologist Charles Rice (PhD ’81) and astronomer Andrea Ghez (PhD ’92).

Rice, who is the Maurice R. and Corinne P. Greenberg Professor in Virology at Rockefeller University, studies pathogenic viruses and innate antiviral immune mechanisms; he received the Nobel Prize in Physiology or Medicine for his contributions to discovering the Hepatitis C virus. Ghez, who is currently distinguished professor of physics and astronomy and head of the Galactic Center Group at UCLA, studies observational astrophysics and received the Nobel Prize in Physics for her role in the discovery that there is a supermassive black hole at the center of our galaxy.

When *Caltech* magazine suggested I reach out to both of Caltech’s most recent Nobelists for a conversation, I was excited for the opportunity to talk to them alum-to-alum, to discover our shared experiences, and to learn from the paths traveled before me.

I’m honored to share their stories here.

CHARLES RICE (PhD '81)

2020 Nobel Prize in Physiology or Medicine: "For the discovery of the Hepatitis C virus."

Q In a year so dominated by talk of viruses, what was it like for you as a virologist to be chosen for the Nobel Prize?

A I think 2020 will be remembered as the year of the virus. Virologists have always had to try and explain to people what the hell a virus is, and we don't have to do that as much anymore. I don't know how much the emergence of SARS-CoV-2 and COVID-19 disease might have influenced the deliberations of the Nobel Committee, but it's a mind-boggling coincidence.

Q You work on hepatitis C. Can you explain the virus and the disease?

A Hepatitis C is a blood-borne pathogen that infects hundreds of millions of people, but many people don't know they've been infected because acute infection symptoms can be relatively benign. Unfortunately, that means that even with the treatments that we have today, there are many people out there who have had the virus percolating in their bodies for decades, and some have developed severe associated liver disease.

It's been called a stealth virus, a silent killer. But there are also people who have been infected with hepatitis C for 50 years, and their livers are fine. Hepatitis C and SARS-CoV-2 are similar in that they can produce very different outcomes in different people.

Q Can you talk about your contributions to hepatitis C research?

A By the mid-century it was known that liver inflammation, or hepatitis, was caused mainly by two viral agents that later turned out to be hepatitis A virus and B virus. The discovery of hepatitis B virus was the subject of a Nobel Prize in 1976. But my co-recipient Harvey Alter showed that there was another distinct form of chronic hepatitis that was caused by neither of these, which he creatively called the non-A, non-B agent. My co-recipient Michael Houghton isolated the genetic sequence of the unknown virus and found that it was a novel RNA virus in the family *Flaviviridae* and named it hepatitis C virus (HCV).

So a virus associated with hepatitis C had been found, but we needed to know if it was solely responsible for causing the disease. At the time, I was at Washington University in St. Louis, and we noticed that in the isolated sequence, a piece of the genome was missing, a piece that is very important for replication. We genetically engineered our lab sample to have that piece and thus be more similar to the virus that was actually circulating in the population. Because our first clones in the lab had variations, we fixed these by constructing a consensus sequence. This lab-made RNA was then shown to launch HCV infection and cause the disease in chimpanzees. This defined the genetic sequence of a functional viral genome and provided a foundation for using modern molecular biology to study the virus and develop new systems for drug discovery. Although this was a very important milestone, there were still many challenges ahead leading to the development of today's drugs, which can cure just about everyone in a few months with a daily pill.

Q What got you interested broadly in science? And why virology and this particular class of viruses?

A I went to college [at UC Davis] thinking that I would be a vet, but I got interested in biology, chemistry, and genetics, and just took a lot of courses.

Between my junior and senior years at Davis, I had a really fantastic summer at the Woods Hole Marine Biological Laboratory. It was intense, basically 24/7 lectures, laboratory research, a transformative research experience. But I still wasn't 100 percent sure that I wanted to do research, so I took a year off between finishing my studies at UC Davis and arriving at Caltech as a graduate student, and became a traveling vagabond for the better part of a year in Central and South America.

When I eventually arrived at Caltech, I had planned to study developmental biology using sea urchins, but I found that I had been placed in the laboratory of Jim Strauss [Ethel Wilson Bowles and Robert Bowles Professor of Biology, Emeritus (PhD '67)], not in Eric Davidson's lab. This was a molecular virology lab studying an enveloped RNA virus called Sindbis virus, an obscure but attractive model virus for studying an RNA animal virus.

That's how I ended up getting exposed to virology. I don't know if the placement in the Strauss lab was random or who orchestrated that. I think if I ended up in an immunology lab, I probably would've ended up being an immunologist.

Q How did your time at Caltech shape or influence your career? And do you have a favorite memory from your time here?

A When I arrived at Caltech, I thought I was going to go to Caltech and do my PhD and move on. That turned out to be totally wrong. I loved the environment and ended up staying at Caltech for about 10 years.

Part of the reason for that was the wonderful atmosphere among graduate students in the biology division. Everybody was so passionate about doing research. People were basically in lab seven days a week around the clock.

But we didn't work all the time. There were softball games and lots of picnics. As I recall, there was also some beer drinking associated with some of those.

I ended up finishing my PhD formally in 1981, but I was having so much fun, I thought I would just stay and keep doing what I was excited about. We had started working on other viruses, including yellow fever, which was the prototype member of what was later a new family of viruses, the *Flaviviridae,* which is the family where the hepatitis C virus landed.

Q Running a lab is obviously a lot of work. And now that you have won a Nobel Prize, there must be even more demands on your time. Do you get tired? What keeps you going?

A I still have a lab of 30 people working on all kinds of different topics. We have studies going on with SARS-CoV-2 virology and COVID-19 disease. I also agreed to be on the New York governor's clinical taskforce, charged with evaluating and summarizing COVID-19 vaccine safety and efficacy for New Yorkers.

It is a bit overwhelming at times, but I'm fortunate. I have some incredibly talented people in the lab who share a lot of the responsibility.

Q In a normal year, what do you like to do when you're not working in lab?

A Growing up in California, I love the outdoors. My spouse and I enjoy taking a break and getting a remote mountain fix. We grab our dogs and drive from Manhattan to a very remote cabin in the Wind River Range in Wyoming. It's one of the most beautiful spots on the planet. There's no internet or telephone, and it's 15 miles away from the nearest paved road.

Q What was it like to get that phone call from the Nobel Prize committee?

A I was by myself in our apartment in Manhattan. It was pitch black, and I thought, "What the hell is going on here? Who's calling me at 4:30 in the morning?"

Then there was this voice with a Swedish accent on the phone. It still didn't really dawn on me at all. I didn't think that there was even a remotest possibility of me winning a Nobel Prize.

It was a pretty strange, surreal experience. And I have to say it still is. It's not something where you can hang up the phone and go back to bed.

ANDREA GHEZ (PhD '92)

2020 Nobel Prize in Physics: "For the discovery of a supermassive compact object at the centre of our galaxy."

Q What led up to the discovery of this supermassive compact object?

A Stellar mass black holes had been theorized for a long time, and now we have strong observational evidence for them from LIGO [the Laser Interferometer Gravitational-wave Observatory]. Roughly 50 years ago, people suggested that all galaxies have supermassive black holes, those that are a million to a billion times the mass of the sun, located at their core.

We set out to prove this. The center of our galaxy was the best place to look because it's the closest center of a galaxy that we'll ever have to study.

The center of the galaxy is obscured by a lot of dust, so you need to go to infrared wavelengths. Having worked at Palomar Observatory during my PhD at Caltech, I knew that the Keck Observatory that was just about to come online in 1993 would be a powerful telescope to observe with.

With large telescopes, the blurring effects of the earth's atmosphere obscure the fine detail. We had to be able to compensate for that, so at first we used a very simple technique called speckle imaging. That allowed us to prove that there were stars in the center of the galaxy and then to track their motions. Then, about 10 years into this work, it became possible to use adaptive optics, which was a much more powerful technique.

We went from measuring just velocities on the plane of the sky to accelerations and then full orbits. From this, we could show that there was 4 million times the mass of the sun contained inside a region that corresponds to the scale of our solar system.

Q What were some of the challenges you encountered?

A We were turned down [on our first request to use Keck to measure these phenomena]. To me, it was just so damn obvious that this was going to work. Then it ended up working out so much better than we could possibly imagine. It had so many phases of excitement: excitement because the first image worked, excitement because we just discovered stars, excitement because the next year we could show that they were moving.

At that point, people started suggesting that there were all sorts of ways that these things could be moving fast without a black hole. So, every step of the project, there was questioning and skepticism. In a sense, that's how science works. You're not supposed to just accept, so it drives you on to the next stage of the project.

As the technology has gotten better and better, more and more results have actually come out. We were able to not only answer the question we set out to address, but we've also uncovered a host of other questions to answer or to think about.

Q What got you interested in science initially and why astronomy, in particular?

A Growing up, I had no idea what I wanted to do, but the moon landing happened when I was 4. In hindsight, that's the thing I like to point back to in terms of the first time I was really inspired to think about the universe, and it really took hold with me. Although, at that time, I also wanted to be a ballerina.

I think it became quite clear that I had an aptitude for math and science. I really enjoyed it, and it was a language that came naturally to me. I just thought of it as a giant puzzle. To me, math and science is that world of just figuring out how to put the pieces together in a logical way. So by the time I went to MIT [as an undergraduate], I felt like I had "found my people."

Q I was excited to interview you today because when I was in high school and applying to college, I wanted to study astrophysics. Looking up women astronomers in Southern California, I came across your name and noticed that you went to Caltech. It feels really cool to finally meet you.

A I love hearing that because one of the things that I really believe is that the best way you can encourage young women into science is by being successful yourself and making that success visible. In other words, really engaging with the public. I remember being an undergrad, at some points I'd look around and think, "Well, there are not a lot of women in this field. Am I on the wrong playground?"

In 1995, I was contacted by a couple [Judith Love Cohen and David Arthur Katz] that writes this series of books: *You Can Be a Woman Engineer,* and so on. They reached out to me and asked if I would be interested in participating in their project, so we worked on *You Can Be a Woman Astronomer*. I was delighted to do so because I've always been interested in encouraging young women into the sciences. I think it's great to engage kids at that age.

Q How did your time at Caltech shape your career?

A Tremendously Caltech is such an amazing place in terms of the resources and the facilities. Certainly, in astrophysics, having access to all those telescopes is just remarkable. Then in the community of people there is just deep intelligence and incredible dedication to science. I'm really grateful for the opportunity I had as a student to work with a truly remarkable scientist, my PhD adviser, Gerry Neugebauer (PhD '60), who was a huge influence.

One piece of advice I remember from Gerry was to have deep respect for the data, paying attention to what the data are telling you without being biased by what you may or may not want to see come out of it.

There are so many pressures today associated with getting the resources that it's really important as a scientist to respect the process, to be patient, and just get it right. I think I learned that discipline at Caltech.

Q Being a principal investigator and now a Nobel laureate must be a lot of work. What keeps you going?

I think it's a true privilege to be able to do this kind of work, to be in a field where you get to set the questions that you're interested in asking.

And then there's teaching, which is so immediate. I'm very grateful to be able to do these two things because I think they complement each other well. Being able to bring forefront research into the classroom is exciting to the students. Then being able to bring students into the research is also really exciting for me because students ask you those basic questions, and they remind you to think deeply about "Why is it that we do it this way?" and "How do we know what we know?"

Q What was it like getting that 2:45 a.m. phone call?

A I think anyone's first reaction to the home phone ringing in the middle of the night is "Is everybody OK?" But then, very quickly, you realize this is a very different kind of phone call. It's breathtaking, kind of unbelievable, and I was just over the moon for days. One of the most delightful things, actually, about getting it during COVID times is it brings such joy to have good news to share.