Sensing touch, the immigrant life and Ardem Patapoutian

The Nobel Prize winner talks about PIEZO 1 and 2, proprioception and the viral photo of him and his son from the 2021 Nobel Prize announcement.

1 November 2023 | by Brady Huggett

This transcript has been lightly edited for clarity; it may contain errors due to the transcription process.

[opening theme music]

Brady Huggett
Welcome to "Synaptic," our podcast that investigates the people, the research and the challenges of the neuroscience field. That's right. The show has broadened. We will cover autism, but now our guests will include all of neuroscience. I host "Synaptic," and my name is Brady Huggett.

[transition music]

For this show, for Episode 7, let's start with the Green Line in Beirut, Lebanon. After the start of the Lebanese Civil War in 1975, Beirut was divided into West and East. West Beirut was mainly Muslim and had both secular and Muslim militias. East Beirut was mainly Christian and had mostly Christian militias. These groups set up snipers and barricades along the divide that split Beirut, and in the dead zone between these factions, where no one lived and people were rarely seen, slowly and steadily a rich green foliage grew. From that, this strip of demarcation became known as the Green Line.

Now, people did cross from one side to the other through specific channels to visit family members who lived just blocks away on the other side, or to buy bread, or to talk with friends. Militias stood at either end of these crossing points, monitoring who passed through. This of course made the journey dangerous. Kidnappings and executions occurred regularly over the years along the checkpoints, sometimes happening in response to each other. You killed one of ours, we'll kill one of yours, that sort of thing.

For our purposes, one night in 1984, a 17-year-old boy named Ardem Patapoutian crossed from West Beirut, where he lived, into East Beirut to spend the night with a friend. That's our guest for today, Ardem Patapoutian. Ardem and his family were Armenian, and Armenians were considered neutral in the war, but when he crossed back into West Beirut the next day, he was stopped by armed militia and held for several hours.

Eventually, he was let go, but when he got home and was safe again, he realized, "I can't live like this." He began to think of ways to change his life. We talked about that on this podcast. We also talked about his journey to America and his experiences as a new immigrant in Los Angeles and the loneliness of that. Of course, we talked about his scientific journey through his discoveries working with the peripheral nervous system and proprioception, all the way to winning the Nobel Prize in 2021. All that is coming up.

Now, I visited Ardem at his office in the Scripps Research Institute, about 15 miles north of San Diego. We cleared a space on his desk, and I set up the mics, and we took a long look at his office phone right next to my recording equipment before deciding to leave it where it was. No one calls me anyway, he said, which I found hard to believe, but actually no one did call during the interview. There was a fan outside his window, so you can hear that a little bit in the background.

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I recorded him on September 22nd, 2023, an overcast but nice morning in Torrey Pines. It was a wonderful interview, I thought. He's a gracious person and patient, or anyway, he was with me. Let's begin here, where I'm asking him how long he's been in California. This should be all you need. Here is your episode of "Synaptic" with Ardem Patapoutian, starting right now.

[transition music]

Brady Huggett
You've been here in California for 30 years plus, right, at this point?

Ardem Patapoutian
That's right.

Brady Huggett
I've done some research, of course, so I know that you actually did not grow up in California.

Ardem Patapoutian
That's right as well.

Brady Huggett
Yes. You were born, I think, in Beirut, yes?

Ardem Patapoutian
Yes. I'm of Armenian origin, and I was born in Beirut, Lebanon. I was there for 18 years before I came to California.

Brady Huggett
This was during —- Well, let's see. The Lebanese Civil War started in '75, right?

Ardem Patapoutian
That's exactly right. Yes. I was 8 years old. I was born in '67. Lebanon was a beautiful country, but most of my memories are post-Civil War, which is sad. I guess one message is if you can survive the war in Lebanon, you can survive science. [laughs]

Brady Huggett
Exactly. You're growing up. Did you have an interest in science when you were young?

Ardem Patapoutian
Not too much. A little bit, but I wasn't one of those kids that, I knew I was going to be a scientist when I was young at all. My parents had "brainwashed" me that I wanted to become a medical doctor.

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Brady Huggett
Well, that's science in a way, yes?

Ardem Patapoutian
That's science in a way. I think mainly for selfish reasons, they wanted a family doctor. My sister and brother were both very scared of cockroaches and stuff. I was the tough one that would go and get rid of them. They're like, "OK, you're the-

Brady Huggett
You're the doctor.

Ardem Patapoutian
-medicine guy." That was my initial link to biomedical research. [chuckles]

Brady Huggett
Where do you fall with the siblings? Are you the oldest?

Ardem Patapoutian
I'm the youngest.

Brady Huggett
The youngest? The youngest and the toughest, then?

Ardem Patapoutian
[chuckles] In some ways.

Brady Huggett
In some ways. You're growing up. When the Civil War happens, when it starts, does your family think, 'Well, what are we going to do? Are we going to try to live through this?" I know that obviously, people left the country then.

Ardem Patapoutian
Yes. It's a bit complicated because of the Armenian origin. We lived in an Armenian bubble. My parents were born in Lebanon, but their grandparents, of course, are the product of the migration because of the Armenian genocide from modern Turkey to Lebanon. Although we were Lebanese, we were, in a way, both acted and treated like second-class citizens. We love Lebanon, love lots of things about Lebanon, but that's — Homeland is Armenia still.

That complicates the equation of what you're asking is, maybe if you felt and or were Arabic you would have hung out more, but a lot of Armenians, I think, were like, "OK," as you said, "do we stay or do we leave?" It took us a long time to leave. After 12 years of being in the Civil War, but we finally left. Of

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course, many people, Armenian and non-Armenians, left Lebanon. It was an interesting but tough childhood.

Brady Huggett
Yes. Do you know who Noubar Afeyan is?

Ardem Patapoutian
Of course, yes.

Brady Huggett
I talked to him and-

Ardem Patapoutian
I know him well.

Brady Huggett
-he was telling me — Right. Your backgrounds are very similar, actually.

Ardem Patapoutian
Very, very similar.

Brady Huggett
Armenian growing up in Beirut.

Ardem Patapoutian
Yes.

Brady Huggett
He was telling me that the buildings were coming down. There were dead people in the street. There were bodies in the street. That was part of his childhood too. You're saying that sounds like that was part of yours.

Ardem Patapoutian
Oh, absolutely. Whenever there were bombs, we used to all go to the shelter downstairs. It's just some really scary stuff. I was even kidnapped by some militias for a few hours crossing West and East Beirut. That was actually the event that made me say, "OK, I got to get out of here."

Brady Huggett
Just you were kidnapped?

Ardem Patapoutian
Yes.

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Brady Huggett
How old were you?

Ardem Patapoutian
I was about 17.

Brady Huggett
Tell me what happened here.

Ardem Patapoutian
You know there's West Beirut and East Beirut.

Brady Huggett
Yes.

Ardem Patapoutian
West Beirut is mainly Muslim; East Beirut is mainly Christians. At that time. Now that doesn't exist. Armenians are Christian. Because we were pretty neutral in the war; we were pretty much the only Christians that could go back and forth as we wished. I stayed the night with a friend in East Beirut and I was walking across the border to West Beirut when I heard gunshots and I started running and some militia folks saw this 17-year-old running towards them. They stopped me, asked for my ID. In a tragic way, in all Lebanese IDs, your religion is written on it. They saw Christians, so they were a bit, some problematic issues there. I think after a few hours, they realized I was not dangerous and they let me go. It was a huge scare for me.

Brady Huggett
As you're running, you say they confronted you. Guns drawn, they confronted you, stop and the whole thing.

Ardem Patapoutian
Yes, absolutely. I think when I got home, that's when I said, "OK-

Brady Huggett
I can't live like this.

Ardem Patapoutian
-I can't live like this." I think the bombs are not personal. Like they fall and you hide. When it's just personally, you get held like that, it's a different effect on your psyche.

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Brady Huggett
Oh, for sure. Yes. All right. You're growing up in this tumultuous childhood where the city is literally under siege at times, and you still think you want to be a doctor all the way through your school.

Ardem Patapoutian
Yes. I was actually at American University of Beirut, which is a wonderful university with an American affiliation. I was, at that time, pre-med student there. I did one year at the American University of Beirut before I-

Brady Huggett
Chemistry.

Ardem Patapoutian
That's right.

Brady Huggett
You're thinking, I'm going to use this to build a career as a physician.

Ardem Patapoutian
Yes, that's right.

Brady Huggett
Right. Then after the kidnapping, you thought, "I can't stay here."

Ardem Patapoutian
Yes.

Brady Huggett
Did your whole family leave with you? They all emigrated at once?

Ardem Patapoutian
It just so happened that my mom's sister was a citizen of the United States. They had applied for us to get a green card, which got delayed and for a long time. Finally, just about that time we received positive response for that as well. We were able to come in as immigrants with a green card.

Brady Huggett
The whole family? Brother, sister.

Ardem Patapoutian
I came first. My sister never came. My brother was too old to get the green card because he was above 18 years old at the time. After a year that I came, my parents came after that.

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Brady Huggett
You were first?

Ardem Patapoutian
I was first with my brother who went directly to graduate school, but he wasn't an immigrant. He was on a student visa.

Brady Huggett
All right. Then you're first. Is your plan to continue medical school? You're leading up to medical school.

Ardem Patapoutian
Financially, we're not very well off. The first thing I did when I came to California is that I wanted to go to public school. You can't qualify for reduced tuition until you're a resident. I had to live in California for one year before going to college. The first year, I just worked at a few jobs, minimum wage, and became a resident. Despite all the difficulties in Lebanon, that was the toughest year, I think, in my life.

Ardem Patapoutian
Oh, I'm sure. You left your country behind, your family behind.

Ardem Patapoutian
Hold on, yes.

Brady Huggett
Well, you had a relation?

Ardem Patapoutian
My brother was in town. For a few months, we didn't have a car. He lived 20 miles away, but we hardly saw each other. [chuckles] Pretty soon we got a car and started living together. That was a huge relief.

Brady Huggett
When you were living separately, were you paying rent someplace, or what was happening?

Ardem Patapoutian
Yes. I was renting in this tiny apartment and working at an Armenian newspaper doing odd jobs. One of the things I remember, actually, is that I didn't have too much money to buy furniture. I just had a makeshift bed. I was going crazy in the silence of this apartment by myself. I went and bought this black and white TV that I still have. I've kept it. It was $60, I remember.

Brady Huggett
With like the rabbit ears on top.

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Ardem Patapoutian
Yes, exactly. This tiny black and white 12-inch TV. There were colored TVs at that point, but I just couldn't afford it. I would just have it on all the time just to keep me company because it was just a lonely time.

Brady Huggett
Anything, news, sitcoms, whatever.

Ardem Patapoutian
Anything, yes. Reruns of "Taxi." [chuckles]

Brady Huggett
You're living there by yourself. You're working — Were you a writer at the newspaper? Or are you just helping put the newspaper out?

Ardem Patapoutian
It's so bizarre to say this. My English was terrible. I knew theoretical English. I had a hard time understanding people because I thought they were talking so fast. I was put in as the English section editor, which is so ridiculous. Every Tuesday, we used to print the labels on the thing, go to the post office, and drop the newspaper. It was a weekly. I even got to write the horoscopes in the newspaper because the editor saw some older lady at an event and she told him that "I'm reading the same thing every few months, the same horoscopes. How is that possible?" He came and said, "Oh, that's embarrassing. We need new material." We should write them.

Brady Huggett
What do you know-

Ardem Patapoutian
I knew nothing about it. [laughs] I started making this stuff up. I was having fun with it because I would write a specific one to a new friend of mine and say, "Hey, read your horoscope." He would come back and say, "I read it. It makes no sense. Why do you think this is relevant to me?" Then I found out that the printer just would cut and randomly put them. I was specifically writing some advice for someone born in a certain month and she would just randomly put them everywhere.

Brady Huggett
Even what you were specifically writing for someone born in a month, you're just making that up.

Ardem Patapoutian
Yes.

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Brady Huggett
Like, this week you should look out for good luck and-

Ardem Patapoutian
Yes.

Brady Huggett
Oh my God.

Ardem Patapoutian
Yes. I apologize for all those people who follow this and think it's some kind of science.

Brady Huggett
You would have to do 12 of those every issue for the month?

Ardem Patapoutian
Yes.

Brady Huggett
Oh my God. That sounds amazing.

Ardem Patapoutian
That was the most fun, actually.

Brady Huggett
Yes. This paper is published for the Armenian diaspora.

Ardem Patapoutian
It's all over the U.S. It goes actually to Boston, New York, LA.

Brady Huggett
Oh, wow. This horoscope was going out all over the country.

Ardem Patapoutian
Yes, absolutely.

Brady Huggett
Not that I've believed in horoscopes before, but I definitely don't now after hearing this story. All right. That was one job that you had just to get the money for the rent while you established residency.

Ardem Patapoutian
Yes, absolutely.

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Brady Huggett
About a year later, you could apply to schools.

Ardem Patapoutian
Yes.

Brady Huggett
Did you apply widely, or just UCLA?

Ardem Patapoutian
I applied to just a couple of schools in LA, UCLA and Cal State Northridge, which is another wing of public school in California system. The idea is if I wasn't going to get into any of them, I would just go to community college for a year and then transfer. I was very fortunate to be accepted at UCLA. Interestingly, the Cal State Northridge, that was my safety school. Didn't accept me. Anyways, it worked out great. I went to UCLA.

Brady Huggett
All right. Obviously, there's a huge culture shock coming from Beirut to LA, right? But also, this is very difficult; you're by yourself; you're lonely. Sounds like a little bit of a language barrier, a language wall you had to deal with as well. When you start school, you're thrown in with all these other undergrads who are probably mostly Americans.

Ardem Patapoutian
That's right.

Brady Huggett
Was it a struggle to blend in with them? How did you manage that?

Ardem Patapoutian
It was. I think for the first three, four years that I came to LA, it was a tough struggle. That's where the Armenian community was so essential, because I was part of the Armenian Student Association at UCLA. That was my social group at the time. Until I started working in a lab, that a little bit replaced it. At this time, my parents were in LA, so I actually moved in with them. I was commuting to UCLA, 20 miles away from home in North Hollywood.

Brady Huggett
They moved over. A year later, they rented a place. You moved in with them.

Ardem Patapoutian
Yes.

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Brady Huggett
Did your brother? No, he was-

Ardem Patapoutian
He was already going off to graduate school. I think he was living on USC campus.

Brady Huggett
As you're at UCLA, you're still thinking, "Well, I'm working towards being a physician."

Ardem Patapoutian
That's right.

Brady Huggett
Somehow obviously that changed.

Ardem Patapoutian
That changed.

Brady Huggett
What happened?

Ardem Patapoutian
It was interesting. UCLA is a very large public school. My classes in biology were 100 to 400 students. I just realized that I need great letters of recommendation to go to medical school, and I wasn't getting to know any of the professors. My idea was to work in a lab, just simply to get a letter of recommendation. I thought I hated research because I really disliked lab courses, both in biology and chemistry. I thought they were boring, not creative, and stressful because-

Brady Huggett
What if it failed?

Ardem Patapoutian
What if it failed? You had these expectations. It never worked out. You had to explain why. There's no joy of discovery, which later, of course, I found that's the whole point of-

Brady Huggett
Science.

Ardem Patapoutian
-working in a lab.

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Brady Huggett
As an undergraduate, sort of like, here's the steps that you do, and you should get this response. Write it up when you're done. If you don't, you have to explain why or where your mistake was.

Ardem Patapoutian
Yes. Exactly. Which I found no joy in. There's no emails. What year is this? 1988. I started calling a bunch of professors and saying, "I want to volunteer to work in your lab." Literally got 10 negative responses. The last one was also going to be, she's like, "No." This is Judy Lengyel; she's like. "No, I don't think we need it." Then right before hanging up, she said, "What's your GPA?" It was 3.7, which is respectable, but not super amazing. She's like, "Come talk to me tomorrow." That was it. She introduced me to two graduate students to help them out. Literally, I fell in love with the whole culture and doing science.

Brady Huggett
Because of what they were doing? You were watching them, and they had joy for science, and you picked up on that?

Ardem Patapoutian
Absolutely. I think it was a dual thing of the actual science, which is, when they described to me that they found this new gene that controls how *Drosophila* goes from a single fertilized egg to this patterned embryo. They were trying to find out how it does it. I was sequencing the gene for the first time. It was just super exciting. On top of that, later on, I've always said I found my tribe in people who do biomedical research.

These were, to me, a super interesting, international group of young scientists. One was from Boston, one was from Iceland, someone was from Italy, and they were all drinking fancy beers at happy hours on Friday. I'm like, "What is this? This is great." Then I found out that you can go to graduate school. Not only you don't have to pay tuition, you get a stipend. For me, that was like, "I get to do this fun thing called research, and on top of it, I get paid. This is heaven." I decided to switch from wanting to go to medical school to graduate school. I got some pushback, actually, from my parents.

Brady Huggett
I was going to ask. What did they say?

Ardem Patapoutian
They weren't very happy about this. Just because they didn't know anything about research and if it was a stable job or if you would get a job, which was actually a correct concern in some ways. My brother convinced me that I don't want to make this decision after four years thinking I'm going to go to medical school. That I should take the MCAT and the GRE and apply to both, and after I got in just make a sane decision that I have an option but I'm not doing this because I'm being lazy and I don't want to go into medical school. I did that, and it all worked out.

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Brady Huggett
You took the MCAT? You did all that?

Ardem Patapoutian
Yes.

Brady Huggett
Did you apply to schools?

Ardem Patapoutian
I applied to schools. I did some M.D.-Ph.D.s, thinking this is in between the two. I didn't get into any of those. I got into UC Irvine Medical School, but I decided to go to Caltech, still in Los Angeles, for a Ph.D.

Brady Huggett
Your parents make peace with this, and you decide, "Well, I'm going to go into research." Then Caltech.

Ardem Patapoutian
Yes. Not too far.

Brady Huggett
Yes. Not too far. Actually very close. Did you know what you wanted to study there?

Ardem Patapoutian
I think I was very interested in developmental biology. I did shift. I went thinking I was going to study transcriptional regulation but then really got interested in this lab of Barbara Wold that they were for the first time figuring out very similar to what I was doing in flies but in a mouse system, the same question of how does a fertilized egg then decide to become a neuron or a muscle cell. They had found these transcriptional regulators called the MyoD family that had the incredible ability that you put it in an undefined, undifferentiated fibroblast and this one gene expression would be sufficient to make this into a muscle cell. This became a new passion, and that's what I spent five years at Caltech studying.

Brady Huggett
Then, when that finished, you went and got your postdoc. I think also you met your wife at Caltech.

Ardem Patapoutian
That's right.

Brady Huggett
Was that in Barbara's lab?

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Ardem Patapoutian
Yes. When I was a first-year graduate student, she was already a senior undergrad, and she did work in the same lab.

Brady Huggett
She had the same excitement for-

Ardem Patapoutian
Yes, absolutely. We both were studying the same thing. That was fantastic. Of course, we've been together since then and it's been a very excellent experience.

Brady Huggett
When did you get married?

Ardem Patapoutian
When I was a postdoc and she just finished her Ph.D. After she graduated, she moved to Berkeley. We did a three-year-of-long-distance relationship, and then I moved to postdoc at UCSF and then we were back together. That's when we got married.

Brady Huggett
Three years of your Ph.D., she was in Berkeley.

Ardem Patapoutian
That's right.

Brady Huggett
You kept it up and then it would be OK.

Ardem Patapoutian
Yes.

Brady Huggett
You finished your Ph.D. and you're looking for a postdoc. Were you looking specifically for one area or one lab?

Ardem Patapoutian
I was looking at the Bay Area because that's where Nancy was and to be reunited in a way. I made a decision at that time either to go into neuroscience or immunology. The idea was that both of those fields were, I think, very exciting things were happening there and both had, in addition to academic interest, translational promise. I tried to read papers in both fields and I thought that immunology was even more jargony than neuroscience [chuckles]. I decided to go into neuroscience. It is intimidating to get into the

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study of the brain from when you don't have any education in it. My plan was to go into the peripheral nervous system where these neurons sense, touch, pain, temperature. It's a simpler system outside the brain. The whole idea was to ease into it. Do postdoc there and then move into the brain.

Brady Huggett
Oh, I see.

Ardem Patapoutian
That was my plan. 28 years later, I'm still in the peripheral nervous system. [chuckles]

Brady Huggett
I get this, like the brain being this, even today, this vast unknown world, right? We're really still trying to understand it. You couldn't have thought that was beyond your means, right?

Ardem Patapoutian
I was a bit intimidated for sure. I think you got to understand that it's not just the complexity of the brain, all the tools to study the brain, which is, electrophysiology, recording of neurons, and stuff. If you haven't done that, it's a completely different concept and it could be intimidating to a Ph.D. student.

Brady Huggett
Oh, sure. Yes. You're thinking, well, if I can study this peripheral part of the neuroscience, I can figure out the tools and then later I can apply them if I want.

Ardem Patapoutian
Exactly. Yes.

Brady Huggett
OK. Good. Then you studied under Louis Reichardt, I think, at UCSF.

Ardem Patapoutian
That's right.

Brady Huggett
What were you looking at in your postdoc?

Ardem Patapoutian
Lou was involved in many different fields of neuroscience. One of them was this family of proteins called neurotrophins. They're amazing molecules where they're growth factors for neurons. The whole idea was that you make too many neurons, survival of the fittest kind of way, only a few of them survive, that get to the right target, get the right growth factors. These were these neurotrophins.

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Some peripheral neurons, for example, express the receptor and send out projections to the skin. If they got enough neurotrophin, they would survive, the rest would die away. It was very Darwinian idea at the cellular level. How these neurotrophins were regulated and what was the consequence of not having them in vivo was part of my postdoctoral work.

Brady Huggett
That takes you to almost 2000, I think, right?

Ardem Patapoutian
That's right.

Brady Huggett
You finished your postdoc and now- You have to decide what's next for your career. You're married at this point, right?

Ardem Patapoutian
That's right.

Brady Huggett
How did you and Nancy decide what to do next?

Ardem Patapoutian
At first, we were thinking that I should wait because I had done enough postdoc work to be able to get a job, but we thought we would wait and look for jobs together. People strongly suggested that if you have a good paper published as a postdoc, you don't want to wait two, three more years because if you're not productive after that, people will question. Nancy very generously encouraged me to look for a position right then and there and said, "We'll figure it out."

I mainly applied to academic places, but it was the middle of the year, so I did a small search. People in my lab now apply to 30, 40 places. I only applied to three places. One of them was this very unique position here in San Diego where Pete Schultz, who has become my mentor, has started a new institute called the Genomics Institute for Novartis Research Foundation, short for GNF.

This is an institute that the Swiss pharmaceutical company has funded, but it was not going to take active role in managing it. We were just going to explore the new genomic data, and they might get some interesting targets for patenting and working on it. It was a fantastic environment, in a way, to do research in a slightly different way.

Brady Huggett
Right, because you're, number one, pharma usually, and Novartis does have some money, so you should have the money that you need to do the work that you want.

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Ardem Patapoutian
That's right.

Brady Huggett
Whatever you want to look at, they're OK with, as long as they get to sort of maybe pick and choose if anything does sort of strike their fancy.

Ardem Patapoutian
That's right. At the time, I had interviewed and had an offer from Columbia University in New York. I told these guys in San Diego that this is great, but the idea was like a Bell Labs. You only have three people in your lab, but you do whatever you want; it's all paid for. They managed to say, "OK, we'll give you a joint offer with Scripps," which Pete Schultz was involved. I got this wonderful dual affiliation. It was 50 percent academic Scripps lab, and 50 percent was at GNF. I started two physically labs next to each other.

Brady Huggett
Oh, you did. I didn't know that. The GNF one is very small.

Ardem Patapoutian
Yes. They had lots of core facilities where you could collaborate and get stuff done. It was very incredible.

Brady Huggett
When you were saying, "Well, I also have this offer at Columbia-" what you were saying was, "I want a bigger group to collaborate with?"

Ardem Patapoutian
Yes. I think in biology, having a good-sized lab is important. I always thought that 8 to 16 is a good number. With only three people, it's just very tough to be very productive. Some people do it, but it's great to have more. Also, as I've learned in my career, is that if you only have three people and two of them leave at the same time, you lose all the connection with the ongoing work. The new people have no one to learn from. I think having a good-sized lab is important for that reason as well, where the turnover-

Brady Huggett
Almost like protective.

Ardem Patapoutian
Yes. Turnover is not as painful.

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Brady Huggett
You said earlier that if you're coming out of your postdoc and you're looking for work and you've had a good paper, you should strike while the iron's hot. What paper had you published that-?

Ardem Patapoutian
We had published a paper in *Science* that showed that this other pathway, the Wnt pathway, controlled one of the neurotrophins, called neurotrophin 3, which was, again, very much required for survival of a special population of neurons, including proprioceptive neurons in this peripheral sensory neurons. It was just connecting two different pathways together. I told you neurotrophins were very important in regulating how many numbers of neurons survive, but almost nothing was known about how neurotrophins themselves are regulated. This was one of the first clues of how that gets regulated.

Brady Huggett
You're setting up these dual labs. Are you still affiliated with the Novartis lab? You still are?

Ardem Patapoutian
No, I'm not, actually.

Brady Huggett
What happened? How did you become fully with Scripps?

Ardem Patapoutian
After Howard Hughes Medical Institute investigator, I became an investigator. That affiliation became a little bit more complicated. As the director change of Novartis, Martin Seidel, and Pete Schultz were very excited to keep this collaboration that I think has served both institutes very well. The new institute head thought that was more problematic in keeping that affiliation. It came to an end.

Brady Huggett
Because these ties to industry.

Ardem Patapoutian
Yes. Of course, after the Nobel, the head of Novartis Research told me that he's so upset that relationship didn't continue till the end because they could have claimed the Novartis researcher becoming the Nobel Laureate.

Brady Huggett
The Nobel. My God, yes. You're building your lab at Scripps then. Solely doing that. Eventually — you just mentioned the Nobel — you do win a Nobel. What work were you doing that led you up to where we are now? You won the Nobel in 2021.

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Ardem Patapoutian
That's right. One of the things I think I realized when I started my own position is that I was very interested in this developmental question of how these sensory neurons become different. How does one neuron decide to sense cold, while another senses pain, while another senses light touch? Very interesting question. It was just this idea that, you know what's even more interesting is how these neurons actually sense warm, cold, touch and pain. This is something that all neurons have to develop and become different.

Brady Huggett
They're specific for each?

Ardem Patapoutian
Yes. How do these neurons actually sense physical stimuli? Pressure is energy. Temperature is energy. How do you translate these physical stimuli into an electrical signal that neurons understand? There's nothing known about that. When I actually started my lab in 2000, just a couple of years before, David Julius's lab had identified the first heat and capsaicin-activated ion channel, which turned out to be the channel that you use to sense noxious heat. We took a genomics approach to find more of these. The first 10 years of my independent work, I made this sudden change, which almost no one does, because everybody assumes that what you did as a postdoc, you have to take that with you and expand on that. It was related. I was working on the same neurons, but the question became very different. My lab identified the first cold-activated ion channel, TRPM8, which also senses menthol, which has this cooling effect. TRPA1, which senses many pungent compounds like wasabi and garlic, as well as other ion channels.

This was work that was also done in David Julius's lab, my lab, and many others. It was a very exciting time where we were finding the same family of ion channels, these transient receptor potential ion channels, each tuned to very different modalities that gives us the sense of both chemical and thermal responses to these stimuli.

Brady Huggett
The idea that there's something for sensing wasabi, is so far, so specific. It isn't specific to wasabi, I understand that. There's other things that it can sense. How have neurons evolved to be that specific?

Ardem Patapoutian
Yes. It's one of the most fascinating stories my lab has been involved in. Most receptors, they sense ligands by this old-fashioned lock-and-key mechanism. There's a pocket on the receptor, the ligand fits, conformational change activates downstream pathways. TRPA1 has evolved to do something completely different. That is, it senses reactive chemicals. Actually, wasabi and the active ingredient in garlic don't have any similarity in their shapes. All they do is react with cysteines. They are reactive chemicals.

TRPA1 has evolved to sense reactive chemicals that it senses through its cysteines and sends the message. The idea is it's evolved to recognize damaging stimuli. Wasabi might not be that damaging, but it fits into

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that little niche of molecular biology, and that's why it feels like burning. Most animals would think of it as pain. We humans, being unusual, have grown to love it. [chuckles]

Brady Huggett
It's the cysteine that is the commonality there.

Ardem Patapoutian
That's right.

Brady Huggett
That is so fascinating.

Ardem Patapoutian
That's why all these ligands that have no shape similarity can all activate TRPA1. When we did screens to find agonists of TRPA1, usually a Novartis would screen 2 million compound libraries and find a handful, maybe 100 activators. For TRPA1, 10 percent of the compounds would activate it almost because there's lots of reactive chemicals out there.

Brady Huggett
Also, when you were thinking about your research, did you just wonder one day, you're like, how is it that- It's such a simple question, and it's never occurred to me until I started looking at your research. How is it that when I put my hand against the wall, this outward pressure creates a current that then tells my body what's happening? Did you just wonder one day how this works?

Ardem Patapoutian
I think the conscious decision in 2000 when I started my lab to focus on these receptors had that in mind already. There was temperature, there's chemical, and there's pressure sensing. Pressure sensing was completely unknown. There was nothing known at the time. As I said, the first 10 years, we worked on these temperature sensors. It was always in the back of our mind, the elephant in the room is these mechanosensors. Not only they weren't known in touch and pain sensation, we didn't know how muscles or blood pressure, all having to do with pressure is regulated.

That was something we were very interested in, but it took us about eight, nine years to start focusing on it because we were so busy working on the temperature sensors, which I think are also very interesting, of course. In science, sometimes you have to look at a field and say, I think the main big questions of temperature sensing are now maybe solved, and the field is getting into more details. I should say this is a very subjective analysis; there are still people doing excellent work on those sensors. For me, what I was interested in them was answered already. Then we made a conscious effort to say, OK, let's not focus on pressure sensing.

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Brady Huggett
Here's the new challenge. Let's figure this out.

Ardem Patapoutian
Yes.

Brady Huggett
If I'm not mistaken, this is Piezo1 and Piezo2, right?

Ardem Patapoutian
That's right.

Brady Huggett
All right. Tell me about working with that.

Ardem Patapoutian
Bertrand Coste, this postdoctoral fellow came to the lab who had experienced recording from these channels. It's a very simple assay where it's whole-cell electrophysiology, you're recording currents in the cells while you actually with a glass probe, poking the cell. If the cell expresses a mechanically activated channel, then just simply gentle poking of the cell will elicit a current.

Brady Huggett
The cell wall?

Ardem Patapoutian
Yes.

Brady Huggett
OK.

Ardem Patapoutian
The plasma membrane of a hex cell, let's say. Initially, we were trying to find these DRG peripheral nervous system neurons that we've been working on for a long time. His Ph.D. actually had recorded from these neurons and found these beautiful mechanically activated currents. Very soon we realized that these are very heterogeneous cells. They're difficult to work with. They don't divide. You have to culture them.

Trying to find it from them was close to impossible with the current techniques. There we made a decision that made all the difference. In science, some people say very correctly, and I agree, you should pick the most reductionist approach to a question that's still meaningful.

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Brady Huggett
As your first question.

Ardem Patapoutian
As your first question. If our interest was to find a mechanically activated channel, why not find it from the easiest system, which in this case would be a cell line that's homogeneous. You can divide and grow it in a petri dish as much as you want, find it from there, and then you go back and say, "Where is this relevant in vivo?" Is it in the ERG neurons? Is it in heart muscle? Is it in other pressure-sensing systems? Maybe hearing. This was the key. Because then, Bertrand just screened cell lines, easy-to-work-with cell lines, and found that this one of them that's heavily used in neuroscience research, called Neuro-2a cells, actually had mechanically activated currents very similar to what was found in the ERGs.

Once he picked that, he used, at that time, a new technique called RNAi screens, which you can knock down one RNA at a time. He made a list of genes that are expressed in Neuro-2a and not in other cells, but could be ion channels, which mainly means that it has to have multiple transmembrane domains.

Somehow made them into a list, and one by one started knocking them out to see if you knock down gene X, would this mechanically activated current go away? It was still not easy because it was such a low-throughput screen.

To test each candidate, it took him about two to three days to knock it down. Just think about it, that his list was 300 genes long. We were ordering primers to knock down 30 at a time. The first 30, all negative. The second 30, all negative. We were starting to get very nervous for his career, because as a postdoc, you can't just have negative data.

Brady Huggett
If you screen 30 and you get a positive, then you go one by one. Is that right?

Ardem Patapoutian
If you get a positive, you stop because it means you found it.

Brady Huggett
In that 30? I see. I'm sorry.

Ardem Patapoutian
What he's doing is knocking genes one at a time and seeing that the mechanically activated currents are completely normal. It's the wrong candidate. 30, 60, and I think we ordered the next 30 saying, after this, we probably should find you another project because he's been there two years already with no data.

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The 72nd one was it. When he knocked down this gene called FAM38A, which is unknown family 38 member A, he saw that this mechanically activated current almost disappeared. That meant that this gene is required for this current.

That was not the end of the story, but it was a huge eureka moment in a way for him and me and the whole lab. Later on, of course, when the next experiment you do is you get the full-length cDNA of this gene and then transfect it in a completely naive cell, and he saw massive mechanically activated currents.

That meant that this gene is both necessary and sufficient to induce mechanically activated currents. In genetics, that's what you want, to believe that this is it. Of course, it took many more experiments to completely convince us, but that was the beginning of the big discovery.

Brady Huggett
You're publishing on this all along the way, I assume?

Ardem Patapoutian
It took a little bit more experiments than I would have suggested to even publish the first one.

Brady Huggett
Eventually, you begin to carve out space in this field and people begin to take notice. You're working with David Julius at this time?

Ardem Patapoutian
No. Honestly, we were competitors when we were working on the TRIP channel. This reactive chemical of TRIPA1 that I mentioned, I thought it was such a bizarre and unique discovery. I couldn't believe it that we were finding out, and yet David had found the same thing. We kept publishing a few weeks apart in competing journals.

Brady Huggett
Were you communicating with each other?

Ardem Patapoutian
No.

Brady Huggett
Or you would just see the paper and you'd go, well, he's done it too.

Ardem Patapoutian
Yes.

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Brady Huggett
At what point did you just go, well, we should stop, maybe we should just work together?

Ardem Patapoutian
That's complicated if you have exactly the same interests. We never got to work together. I think my big advice to people coming up in the field is — I'm being completely honest here — is that it was a competitive environment between David's lab and my lab.

To me, that was a negative feeling, that we were competing. Looking back now, I feel like we really, at least from my perspective, we enabled each other. I think there's this negative thinking of competition, but it's actually such a positive thing.

The way to think about it is that we're finding out these novel genes and novel mechanisms, and how wonderful it is that within a few months you find that someone else has done exactly the same thing and found the same results.

Sometimes when you don't find the same results, you keep looking at it and find out what's really happening. This idea of competition as a bad thing is something I experienced during the process, but now look at it as a wonderful thing.

Brady Huggett
Meaning that it spurred you on?

Ardem Patapoutian
That's right.

Brady Huggett
Yes, it kept you on your toes.

Ardem Patapoutian
Kept you on your toes, but at the same time, as I said, science is not real until it's replicated by others. We were getting instant gratification in a way.

Brady Huggett
That you're right.

Ardem Patapoutian
That you're right. When you publish a few weeks apart completely independently, that's instant verification, and it's a good thing for science.

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Brady Huggett
Yes, we're on the right path is what that means.

Ardem Patapoutian
Absolutely.

Brady Huggett
I'm going to jump ahead. The Nobel Prize happens in 2021, and some of this is out there, so we don't need to get into all of it. This was a pandemic year, right? I know that- Just briefly tell me, so the way that it works, of course, is the Nobel Committee decides, and then they call the people.

If you're in the United States, for instance, it's usually very early in the morning because of the time difference. They were trying to do that with you but couldn't get through. Just tell me that story.

Ardem Patapoutian
That's right. Like most normal people, I have Do Not Disturb on my iPhone, which means it can't get through when I'm sleeping. Yes. They were calling at 2:00 a.m., couldn't reach me. They have someone there, I found out later, who specializes in these emergency situations to find someone close to you.

They were Googling Patapoutian, California, and they found this other number that they called. It was my father, who's 94 years old. His landline rang, and he answered, and he yelled at them first of why they're calling so late at night.

Brady Huggett
"Who is this?"

Ardem Patapoutian
"Who is this? Why are you bothering me? What are you selling?" I think he quickly realized what was going on, and then he was able to contact me.

Brady Huggett
Because he's on your safe list or whatever.

Ardem Patapoutian
Because he's on my safe list.

Ardem Patapoutian
Yes. When I looked at my voicemails, there's three missed calls from Stockholm. I figured out what's going on. I was able to connect with Thomas Perlman, the head of the committee, just before he announced it publicly. I was able to watch it on my computer, the announcement.

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Brady Huggett
Two things. One is, do you know when you're in the running? I've always wondered this. Does the Nobel say — I don't think they do, right? They don't say there's like six researchers we're considering this year.

Ardem Patapoutian
No, they don't.

Brady Huggett
You had no idea?

Ardem Patapoutian
No, I did have an idea. It's a complicated answer, so bear with me. People tell you. People tell you either that I think this is-

Brady Huggett
Your year.

Ardem Patapoutian
Not your year. You don't know that. They say you're under consideration. Other people, maybe they should or shouldn't say, but they say, I've nominated you.

Brady Huggett
All right.

Ardem Patapoutian
You know that it's in the works. Also, David and I have won a couple of prizes before that.

Brady Huggett
You won a Kavli Prize.

Ardem Patapoutian
The BBVA, the Kavli. It would be very naive to say I had absolutely no idea. You don't know the year. Also, philosophically, although I knew, I've put it aside. I didn't want to become one of these people who either lobbies for it or fixated on it or consider that a goal, like didn't want any of that to happen to me.

That's why I wasn't going to undo my Do Not Disturb that night. Completely honestly, because of the COVID that you mentioned, like many others, I thought it was going to go to something related to COVID research, either the vaccines or identifying.

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That year to me sounded like that's obvious. Now that I know the process more, I'm not surprised that they haven't given one to that also because the amount of research they do is mind-boggling. They take this so seriously.

Brady Huggett
The Nobel Committee.

Ardem Patapoutian
The Nobel Committee. Afterwards, they told me that they had a file on me for 15 years.

Brady Huggett
Oh, wow.

Ardem Patapoutian
That for COVID, I'm sure they're doing-

Brady Huggett
It takes a while.

Ardem Patapoutian
It takes a while to make sure that they're giving it to the right discovery and to the right people. People have to realize it takes time.

Brady Huggett
Because of it being COVID, normally what happens is, they announce who the winners are, and then there's a press, sort of the press descend on the house, and someone's there with a camera and all that. That wasn't going to happen because of COVID precautions.

I think they reached out to you and said, "Look, we're going to announce this online, and is there a way that we can get some sort of photo of you finding out or seeing this online?" What happens is you're in bed, I think, because it's still early.

Ardem Patapoutian
2.30 a.m. Yes.

Brady Huggett
You're in bed with your laptop watching, and your son is in bed with you, and your wife snaps this photo. It's a great photo. It's like you have just looked up at the camera, and your face is, it's not like, what do I want to say? You're not shocked, because you'd already got in the call, but it's like a bemused tranquility or something, right? You're like, "Well, there it is." Your son, he's got his hand on your shoulder, and

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he's looking at the screen; he's like, "That's my dad," right? I thought that was a very touching photo. It got quite a bit of stir, I think, online.

Ardem Patapoutian
It is my favorite photo for many reasons. One of them is the look being next to Luca, my son. I always joke around that he doesn't affectionately touch me like that all the time.

Brady Huggett
You have to win a Nobel.

Ardem Patapoutian
I study touch sensation, so it all comes together. Whatever you say about Twitter and social media, in the absence of direct human contact, that's how I connected to the scientific community throughout the world with that photo.

That was the introduction of it. As well as, the Lebanese and Armenian community who have been so proud of this. All happened through the social media and that photo. It does have a very special place in my heart.

Brady Huggett
Yes, I would think so. I don't know if your wife spends a lot of time taking photos, but it was almost perfectly placed in the frame. It was really nice.

Ardem Patapoutian
She's very good at it.

Brady Huggett
Yes. Right. There's a few things I want to ask you.

Ardem Patapoutian
Sure.

Brady Huggett
The Nobel happens, right? This has put an amount of notoriety on you, right? The world is sort of looking at you now, and they sort of know your name. If they didn't before, they certainly do now. You're etched in history, right?

It seems to me, just tell me if I'm wrong, since then, you have sort of, I don't know, it's like it's almost freed you up a little bit. There are things you said in the past that when you first came to the U.S., you're like, "I have this long name, Patapoutian, and maybe I should shorten it."

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Or that you didn't want people to know that you'd gone to the American University of Beirut for some reason. Then you're like, I'm not going to do that anymore.

Ardem Patapoutian
That's right. I think the liberating term that you used is just so apt. I think it's this, I also say things like, when I used to go to scientific conferences, I used to have a little bit of a chip on my shoulder, like an agenda, in the sense that, ooh, I should meet this person who's famous. I should get to know this person who might be useful for us to collaborate with or something like this.

Nobel being the ultimate in external validation, I feel like I don't need that anymore. Both whether it's conferences or in the lab, it's gone back to the original reason why I got into science, which is the joy of discovery.

It's just this wonderful feeling that I don't have to prove myself anymore and I can just enjoy discovery, which is what we all get into science to do. What I would love to do is to give this advice to younger folks doing science.

Of course, it's easy for me to say this after the recognition, but I truly believe that, without receiving that validation, you can have this mentality to do what I'm doing now to a certain extent. You can tell yourself that I'm not going to stress out if I don't get every grant, or if I don't get respect from this one scientist, or if I don't get this paper accepted. Just focus on what you love about science.

Again, I say this with lots of hesitation because someone will listen to this and say, "It's easy for you to say. If I don't get my next grant, I can't do science." I understand that. I'm not saying completely forget about practical matters.

I think even if you move the needle a little bit towards more towards the joy of doing science, then you'll be a much better scientist and happier doing it.

Brady Huggett
Yes. All right, I want to ask this because you mentioned earlier in Beirut, Armenians are sort of, you said, I don't know, second-class citizens, as you said. Then you come to the U.S. Immigrants feel like an outsider. Have to learn the language, fit in. You're again, sort of, like outside. Is that part of the chip that you said you had on your shoulder?

Ardem Patapoutian
Absolutely. The example that you gave about, which I admitted to, is that when I first came because of my name and, Beirut, Lebanon, are just jokes about terrorism. I did not mention that I was at American University of Beirut for one year. Just put UCLA graduation.

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Again, what I've noticed is, after the Nobel, I've gotten so many comments about other immigrants who look at me and say, "Oh my God, there's hope for us because I feel like I don't belong. I have imposter syndrome. Then this guy that wasn't a genius in biology with a pedigree of Harvard and MIT came here poor and made it, so I can do it, too."

I never thought of myself as being a role model in that sense, but almost got- I don't want to say forced into, because I do it gladly. Seeing that response gives me so much energy. My whole Twitter account- I refuse to call it X- is one of the goals is to do that, is just show that I wasn't very special, and I've made it and you can, too. That seems to really resonate with people. I love that, actually.

Brady Huggett
Yes, I had this thought, too, that as you get older, when you're young, maybe you're embarrassed about parts of your life. I don't have this degree or my parents were this or a parent was in jail or who knows what it is.

When you get older, you realize that everybody's life has got things that maybe they're not proud of. It's fine. You've got that reached that point where like, it doesn't matter.

Ardem Patapoutian
Yes. Also, just sharing failures or sharing all this stuff you think sometimes is a bad thing. People love that. I think you'll be more appreciated and understood better if you talk about those things.

Brady Huggett
Yes. I guess if you had, as a scientist or whatever in life, if you had just failed, failed, and never won the Nobel, it's a lot harder to put that forth. When you actually got the validation, as you said, look, I was, you might see me.

Ardem Patapoutian
That's exactly right. That's why I'm very careful in saying I don't want someone to think that, yes, you've got the Nobel, now you're telling me I should do this and that. I don't want to come off like that. As I said, it's just a matter of where the needle is. It's just understanding this, dealing with it, and keeping the joy of discovery is very important for scientists, I think.

Brady Huggett
All right. Two things left. The U.S. has had this long issue with immigration. Administration after administration has just kicked it down the road. They haven't really tackled it. I live in New York, and our mayor has said we're having an immigration crisis. The shelters are full, right? I'm wondering, when you talk about immigration, what your feelings are about it?

Ardem Patapoutian
All I can say is that I've experienced it. It's very tough. Part of that, going through that difficulty, really

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prepares you to take on other difficulties in life. There was actually this one article, I don't remember the exact percentages, a huge percentage of people who've won the Nobel. Not that that's just a very important criteria, but it's a fact, that are immigrants.

I think there is something about it. I think it's something about the drive, something about experiencing something and then experiencing something else and the knowledge you get from that.

I feel like, even in science, forget about immigration from country, people who change fields seem to do better because they look at a new field with a new perspective, with a new frame of mind. I think this movement, this change, whether within scientific communities or within countries, is such a great driving force for discovery, and it should be encouraged.

Brady Huggett
Final question. I also saw that you said- I think this was maybe in your comments to the Nobel Committee, but there is nothing more exciting, there's no more exciting sentence in the world than somebody standing by a microscope and saying, "You've got to come look at this." You still feel that?

Ardem Patapoutian
Absolutely. I think this comes full circle to what I was saying of now doing research for the love of discovery. I have to sit down and think, "What is it that I like the most?" I often say no to administrative jobs because I love that, being in the lab.

I used to travel to 12 trips a year, and I have kept that. I don't do more than that. Part of it is to have these discussions with students and postdocs, and once in a while, ask to go and look at a microscope with an incredibly unexpected result. That's the biggest science joy that I still experience.

Brady Huggett
Perfect. Thank you very much.

Ardem Patapoutian
Thank you. This was fun.

[transition music]

Brady Huggett
I really enjoyed that interview. I learned a lot, both about science and how to better consider my place in the world, I think. Maybe you did too. I don't know. Thank you, Ardem, for making time and allowing me to set up in your office.

Sensing touch, the immigrant life and Ardem Patapoutian

The Nobel Prize winner talks about PIEZO 1 and 2, proprioception and the viral photo of him and his son from the 2021 Nobel Prize announcement.

1 November 2023 | by Brady Huggett

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Some of the information on Beirut, the Lebanese Civil War, and the Green Line was taken from a short video produced by *Timeline*, which examined the work of Lebanese photographer, Patrick Baz. Our theme song was written and performed by Chris Collinwood.

I will talk to you on Episode 8, which I've already recorded. Yes, here comes the music to take us out.

[ending theme music]

Brady Huggett
I think we're ready.

Ardem Patapoutian
What's your background?

Brady Huggett
You mean like professionally?