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People & Ideas

Brian Chait: Master of mass spectrometry

Brian Chait builds mass spec machines to probe the depths of cell biology.

Brian Chait

Mass spectrometers can determine the composition of practically any sample, and are thus invaluable for cell research. To build a mass spec requires a deep understanding of physics. You need to know how to break down molecules into their constituent charged ions, how to make these ions fly through a vacuum, and how to catch them and measure their mass. Luckily for cell biologists, Brian Chait knows how to do these things.

"The physicists didn't have a clue what we were doing; they thought that Ken and I were slightly nuts."

Chait doesn't just build mass spec machines; he uses them to investigate cellular biology. He has mapped protein–protein interactions (1), helped determine the structure and composition of potassium channels and chromatin complexes (2, 3), and detected the proteins secreted by microorganisms (4). He is probably most renowned, however, for his extensive work in collaboration with Michael Rout in determining the composition, architecture, and mechanism of the nuclear pore complex (5, 6, 7).

Talking to Chait in a recent interview, what's evident is his all-encompassing passion for science and nature, whether he's describing the inner workings of a mass spec machine, marveling at the mechanics of the nuclear pore, or reminiscing about the stunning mountains and coastline of his native South Africa. What's also evident is his modesty.

SKIPPING SCHOOL

Thanks for speaking with me.

Are you sure you really want to do this article? I don't consider myself all that interesting. I've just put my pants on in the morning and done a few things. I'm no different from anyone else.

I've heard otherwise.

Okay, why don't you ask a few things, and then you can decide whether you've got yourself a story. But you will not hurt my feelings if you decide not to do this.

Sounds like a plan. So then, how did you get started in science?

Like all children, I used to lie on rocks and look in rock pools and dream and watch stuff. The natural world is fascinating, and you can explain almost none of it, yet one seems to want to explain it a little bit. Nothing has changed for me since those early times.

To my slight advantage I think, I didn't take school seriously. I looked upon it as a prison and a waste of time. I think at school they thought that I had a brain defect or something because I didn't take part in much. The whole thing was just too peculiar for me—having to sit in rows and wear shoes.

It sounds inhumane.

It *was* inhumane. [*Laughs.*] Most of the teaching was by rote, which I don't think is terribly helpful. You might get good marks in school, but it's mind numbing. So I didn't go to school much. Instead I explored a lot of things on my own. Well, I did some exploring and also a lot of surfing!

I'm not saying that schooling is universally bad. My children, who went to school in Manhattan, had good experiences. But where I grew up in South Africa, many of the schools were terrible. They were segregated government schools, and mine was for boys only, so it was segregated on all kinds of levels.

What was it like growing up in 1950s Cape Town?

To some extent, when you were young and white, you were shielded from many of the effects of segregation. As I got older, I began to realize what was going on and how terribly unfair and politically disastrous a place it was. I had a comfortable life. But from an ethical point of view, it was a disaster.

TO BRITAIN AND BEYOND

After university you headed to Oxford for your Ph.D. Why there?

At university I studied physics, chemistry, and math. But I wasn't clear on where to go next. My professor encouraged me to do a graduate degree. He hooked me up with a young physicist, called Udo von Wimmersperg, working in Cape Town. We talked for a couple of hours, and by the end of our discussion, I decided I'd do an M.S. with him in nuclear physics.

It was actually going reasonably well, but then Udo went to Oxford to do some work, got involved in an experiment there, and never came back!

In the meantime, my girlfriend went to England for a year's study. So I decided I'd join her. I got accepted to do a Ph.D. at Oxford University, and off I went.

You followed the girlfriend, not the supervisor?

Yeah, and we're still together, Jos and I. So that all worked well!

I liked Oxford. They treat you like an adult. They basically leave you be and see what comes out of the three years. I thought it was a pretty nice system. It's different from America.

What was your thesis about?

It was something called the nuclear rainbow effect, which is the diffraction pattern created by one nucleus scattering off another. It's interesting stuff, but I was quite socially conscious, so I wanted to play a bigger part in helping the world.

I heard there was a job at the University of Manitoba, Winnipeg, with a guy called Ken Standing. He was beginning to apply nuclear physics to agriculture. Jos and I thought going to the prairies of Canada with all that sky would be lovely. So I wrote to Ken, and he accepted me.

Ken and I built an apparatus to measure the protein content of wheat. But I began thinking that looking at specific proteins themselves might be more interesting.

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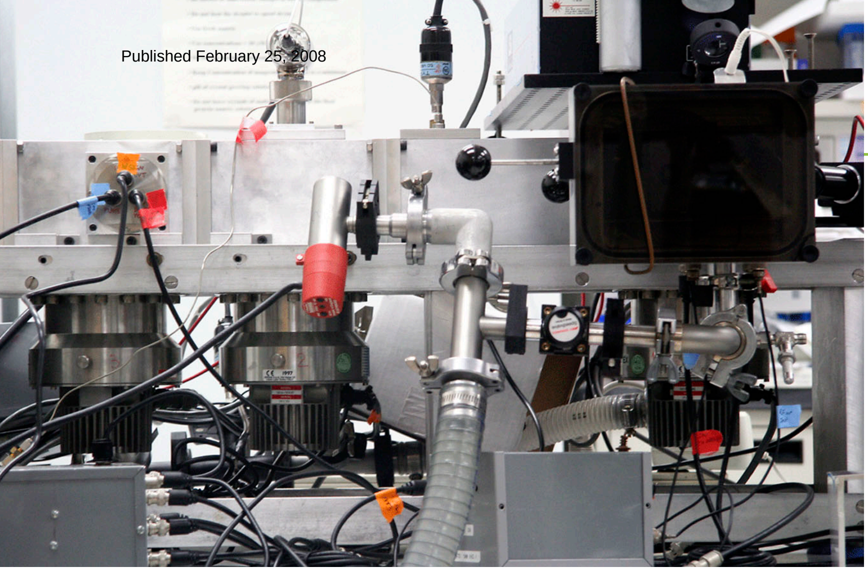

Chait's latest mass spec machine: "Where did you say the sample goes, Brian?"

That is how you got started in mass spec?
Yes. At that time two nuclear physicists, Ronald McFarlane and his colleague David Torgerson, discovered a way to make big molecules, like proteins, fly. This had been a problem in mass spec.

I chatted with Ken, and he agreed that it would be a good idea to use the same method to look at our wheat proteins. We wanted to build an apparatus, but we were poor. An older guy in the department loaned us some money. We had instrument makers at the university who could build things, and I could pretty well steal all the electronics from the nuclear physics department. So for very little money, I constructed a device.

We also needed something called californium-252 as an ionization source. It's pretty nasty—about as dangerous as you can imagine, from a radioactivity point of view. I wrote to the Savannah River Site, a nuclear materials processing center in America, and they sent me a bottle of the stuff, just like that. I think it cost about $100.

Wait! They were willing to sell it to the Canadians?
Yeah, to a postdoc! Amazing. Times have changed since then.

In the meantime, though, Alfred Benninghoven in Germany found that he could make amino acids fly using low-energy ions instead. I thought maybe that would work for our stuff too and wouldn't be so dangerous. So I built an apparatus that used a little cesium ion gun, and it worked.

By this point, though, I had spent three years constructing the thing, and we couldn't get any more money to do actual experiments. The physicists didn't have a clue what we were doing; they thought that Ken and I were slightly nuts. And to the chemists and biologists, we were off the radar. Ken said to me, "You better poke around for a job, because I don't think we're going to be able to pay you." By now I had a little family of four to support.

ROOTED AT ROCKEFELLER

So what did you do?
I heard that Frank Field down at Rockefeller was trying to build a similar apparatus. Frank needed somebody to help him, and I knew how to do it. I came to Rockefeller and worked a second postdoc, and I've stayed here ever since.

Before coming, I knew nothing about New York. It seemed like some kind of esoteric place with big buildings. I was interested more in mountains and sea, like where I grew up. But this job opportunity came up, and I needed to find something, so I talked to friends, and they encouraged us to go down and visit.

It was summertime when I interviewed for the job, and New York seemed alive. I heard music streaming out of windows, I saw a guy running down the street holding a big stereo he'd just stolen, there was a group of people running after him. I thought, "Gee, this is fantastic!" To me, compared with the barren winter nights in Winnipeg, where you'd be lucky to see one person, this was like a big party. It was chaotic.

At first, Jos and I thought, "Is this really a place you can bring up children?" There didn't seem to be any trees or anything. But the boys were soon lying on their stomachs, looking at ants and stuff, and we realized there was no problem at all.

At Rockefeller, you were finally able to blast apart proteins. But you soon moved onto blasting apart bigger complexes.
From the beginning I thought it's not just about building interesting machines, but also about the biology. When I began to look at things like the nuclear pore complex, I got as interested in that as in constructing mass specs.

The nuclear pore work started because Mike Rout asked if I could help him identify the pieces of this pore apparatus. He told me why the nuclear pore is interesting and what it does. It didn't take much to convince me that it was important to study.

From that research, we got an inkling as to how the pore might work. I said to Mike, "If we think we know how it works, we ought to be able to build one out of plastic or something." So I got a postdoc, Tijana Jovanovic-Talisman, to come work with me, and I think she's built one. It's an artificial pore that sorts molecules and decides who's allowed to pass through—much the same as the real thing.

What else are you working on?
We're also tagging specific proteins in viruses and then pulling them out of the cell at regular time points after infection. It allows us to follow the cellular proteins that the viral proteins interact with, all the time using mass spec as a readout. We have some intriguing data on HIV using that approach.

On the machine front, we're continuously designing and building. We've designed all manner of mass spec apparatus over the years. Sometimes, very simple things have been useful—like the pipe we designed for electrospray. It's probably used in about half of all the mass spec machines in the world now, and it started out as just a little hot metal pipe that we wrapped heating tape around. It's not Einsteinian stuff. We've poked around, we've made mistakes. But you've got to keep on working. JCB

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