

A conversation with Oliver Smithies

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Conversations with Giants in Medicine

Oliver Smithies of the University of North Carolina, Chapel Hill, and 2007 Nobel Laureate, is best known for pioneering the techniques required for introducing DNA into cells. His work with gene targeting revolutionized biomedical research and allowed for the creation of knockout and transgenic mice. Smithies's lab itself created the first models of cystic fibrosis, and his further work has gone on to identify many of the genetic factors involved in atherosclerosis, heart disease, and other disorders. To watch the full interview with Smithies (Figure 1) and hear his many stories, see the JCI website (<http://www.jci.org/videos/cgms>). JCI: What were you like as a child? Smithies: I was born in Halifax, Yorkshire, in the North of England. We lived in quite a small village; the total population was only 1,500. I had a twin brother, and my father was an insurance salesman for the Canadian Life Insurance Company. My father was very good with his hands, and we always had a car that was constantly breaking down, so I learned how to use my hands from him. My mother was a teacher in the nearby technical college; she taught English Literature and English and would often read to us. At age seven, I got rheumatic fever, and in those days, people didn't know what to do and there weren't antibiotics. I [...]

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Smithies: I was born in Halifax, Yorkshire, in the North of England. We lived in quite a small village; the total population was only 1,500. I had a twin brother, and my father was an insurance salesman for the Canadian Life Insurance Company. My father was very good with his hands, and we always had a car that was constantly breaking down, so I learned how to use my hands from him. My mother was a teacher in the nearby technical college; she taught English Literature and English and would often read to us.

At age seven, I got rheumatic fever, and in those days, people didn't know what to do and there weren't antibiotics. I was put in bed for 10 weeks. Afterwards, I wasn't allowed to play sports for many years, but it was sort of a benefit because it made me do other things, like reading.

JCI: And tinkering. You spent much of your time making radio-controlled boats and loudspeakers. Did that lead to an interest in the physical sciences?

Smithies: I'd always wanted to be a scientist, even from quite early in life, although I didn't know the word. I knew the word "inventor" from reading while I was sick — I read a comic on an inventor and I thought that was what I wanted to be.

JCI: And yet you landed at Oxford for medical school?

Smithies: I had very good teachers in high school. The chemistry teacher was a

very earnest and staid person, but the math teacher was an awful man. I didn't like him, but he loved mathematics and taught calculus in a way that made it magical. In fact, I never did any more mathematics the rest of my career. When it came time to apply for university, I got my scholarship to Balliol College, Oxford, because I was good at physics and math, and I thought I was going to be a physicist.

But for a reason that I don't remember, I decided instead to go into medicine and did a couple of years in anatomy and physiology, and in the third year, got an honors degree in physiology. In that third year, I was exposed by my tutor Sandy Ogston to a new discipline, which at that time didn't have a name, but we would now call molecular biology. This was a marvelous field, but I thought I couldn't really do a good job if I didn't know chemistry. I took a second degree in chemistry, and that was very fortunate, because it meant that I had background knowledge in animal physiology and medicine and in chemistry. I was never frightened of either of them.

JCI: At what point in your training did you decide to come to America?

Smithies: Well, that was at the end of my PhD. Ogston suggested it would be a good idea if I went to the States for a postdoc, and I wasn't very keen. I said, "I don't like America." To which he replied, "That's a silly remark. All the more reason you should go." There was another graduate student, a visiting Rhodes Scholar from the University of Wisconsin, who suggested going to Madison, Wisconsin, as there was a good physical chemistry department there.

JCI: What did you set about studying there?

Smithies: They had prepared a high concentration of a protein called β -lactoglobulin, but they hadn't been able to crystallize it. I just took the beaker in which the oily substance was and scraped the side with a glass rod; that makes little tiny flakes of dust that are flat, and they act as a seed, and it crystallized. I made my reputation by crystallizing their β -lactoglobulin, and then I

began to study it in different ways than what they were doing. One of them was with the ultracentrifuge, and they had a complicated Tiselius electrophoresis that I used for some studies on solubility and so on. I accumulated a nice set of completely unimportant data. My postdoc work maybe got four citations; my thesis work was never cited either. Neither had anything significant in them, but I learned to do good science.

I had gotten engaged to an American girl, and she didn't want to go to England, and so I got a job in Canada. So in a sense, I moved to Canada for biological reasons. The person who hired me (David A. Scott) said, "You can work on anything you like as long as it has something to do with insulin." I decided to look for a precursor, although I never found it.

JCI: How did this lead you to starch-gel electrophoresis?

Smithies: I found that when I tried to study insulin by filter paper electrophoresis, insulin stuck to the filter paper and it was very frustrating. I heard that people were using a new method with starch grains, and the proteins didn't stick. The only problem was, in order to find out where the protein was, you had to cut a block of moist starch grains into 50 slices and do a protein determination on every one.

I remembered "helping" my mother do the laundry as a child, and she would take starch powder and cook it up with water, and it would make a gooey liquid, which then she would smear on my father's shirt collars when she was doing the laundry. When she later ironed the shirt, the collar was stiff. But when tidying up, I noticed that the gooey starch had set into a jelly. I went back to the lab on a Saturday and found some starch in somebody's chemical storeroom, cooked it up, and found that it did make a gel at a rather high (15% starch) concentration, but the insulin moved beautifully; it didn't stick. And so I invented starch-gel electrophoresis.

JCI: It was also your idea to use vertical lanes.

Smithies: Up until that point, all gels were run horizontally, and I was having trouble with getting the sample neatly into the gel because proteins inserted into an open slot in the gel would move down to

the bottom, and so the gel comes out with a funny migration. But if you turn it vertically, you don't have that problem; so yes, I did invent vertical electrophoresis.

JCI: During this time you learned much more about molecular genetics.

Smithies: I had been running samples from my own serum and from two of my male graduate student friends. I had a pattern that I knew was fairly constant. And then I ran a sample from BW, and BW's pattern was very different, with many extra bands.

JCI: BW was Beth Wade.

Smithies: Yes, and I thought, "I've found a new way of telling men from women!" I called one the M pattern and the other the F pattern. I tried a male and female sample for several days, and the pattern always fit, and then the next day, I tried with a new male friend, and the pattern was the wrong way around; the man had changed into a woman. We teased him mercilessly.

JCI: How did you figure out that what you were actually looking at was haptoglobin?

Smithies: Either Carl-Bertil or Anna-Brita Laurell wrote to me saying, "Do you know, Oliver, the protein that you're looking at, the hemoglobin-binding protein, it's probably haptoglobin, described by Max Ferdinand Jayle." Jayle had described a hemoglobin-binding protein in plasma serum, and he'd even recognized that there were differences in this protein, but he hadn't realized that they were genetic differences.

JCI: So where along this path did you end up back in Wisconsin, thinking about homologous recombination?

Smithies: My wife at the time wasn't very happy in Toronto and wanted to go back to the States, and by then I had done the genetic work with haptoglobin, so I had become, as it were, a molecular geneticist, and I didn't have much difficulty getting a job in Wisconsin. I went back, now in the medical genetics department. Science moved on, and it became possible to sequence proteins, isolate DNA, clone genes, sequence DNA; my lab sequenced the second human gene to be cloned. We had the globin gene in a test tube, and out there were people with sickle cell anemia. I thought, "Maybe I can use good DNA to correct the mutation in globin in sickle cell anemia," but I didn't know how to do it.

It had been possible to place genes in yeast, but the genome is more than 100

times bigger in a human, and I think people thought it wouldn't be possible. But I was thinking about doing it. I came across an article in 1982 that used a rather complicated way to isolate a transforming gene.

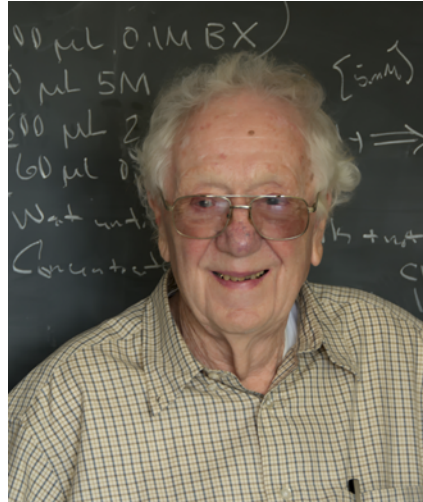


Figure 1. Oliver Smithies on July 28, 2015.

Image credit: Jillian Hurst.

The investigators (Goldfarb et al.) used some very pretty tricks to isolate the transforming gene, and I thought I could use the same general type of method to show if gene targeting worked. I wrote a page in my notebook, which I'm very proud of, in which I wrote how our aim was to develop an assay for placing DNA in the correct place, and that was a pretty important page in my notebooks. The method that I outlined there, in fact, worked. It took three years, but it did work eventually.

JCI: You strike me as being incredibly persistent.

Smithies: I didn't have any people helping me at the beginning of this work, except for a graduate student, but she decided the project was too risky and quit. At a later stage, when I did have help, we realized that we had the possibility of contamination with a bacteriophage and people got very despondent about that.

I went away for a week with my flying friends and came back refreshed saying, "I'm going to start again." So I started again and changed the methods and, together with my postdoc Ron Gregg and other collaborators, we made it work. You have ups and downs, and keeping good notes was important, because there was

part of the assay that required large numbers of bacteriophages, which make little pinholes in a bacterial plate. For some reason, my plaques got smaller and smaller, and I couldn't understand why it wasn't working anymore. I went back and found a little tiny note, bottom right-hand corner of the page where it last worked, saying that the bacteria that I was using to grow the bacteriophages had been made on Friday, and this was Monday. I thought that I had better freshen them up, so the little note says, "Freshen them up by diluting them and letting them grow." They went back into growth instead of being in what we call "stationary phase." When they were growing exponentially, it turned out they made big plaques. So I went back to my bench and changed to growing the bacteria freshly; it worked again. All because of a note in the corner of my notebook.

JCI: Your persistence led to your work being recognized by the 2007 Nobel Prize in Physiology or Medicine. Did that recognition change you, your science, or your approach?

Smithies: Howard Temin got the 1975 Nobel Prize for his work in reverse transcriptase when I was also there in Wisconsin. I remember when he got the Nobel Prize, going to him and saying, "Howard, I hope it doesn't change your life too much," and that's what I felt when I got it myself. It was 20 years after I'd done the work, I was already getting pretty ancient by then, and I didn't really want to change my life, so the answer is, it didn't change my life very much. I think it made it harder for me to get grants, not easier, but that's a purely psychological thing.

JCI: Beyond your famous love of flying, do you have a favorite pastime?

Smithies: I have a favorite composer, Johann Sebastian Bach. I used to play the flute, not very well, and I quit some while ago, but I listen to Bach's music, and I visited where he was born earlier this year.

JCI: Musician, mechanic, writer, pilot, what do you think you would have chosen if you could not have been a scientist?

Smithies: I would love to have been born as Johann Sebastian Bach. I think he had a grand life. He had all sorts of problems; he got put in jail at one time because he was too obstinate about something or other, but that's a life I would have loved to have lived.

Ushma S. Neill