

## Oliver Smithies: Born Inventor

Ruth Williams

*This profile of Oliver Smithies highlights many of the qualities of a great scientist: a down-to-earth, unassuming style (remember “the smaller the mind, the greater the conceit” as I wrote last year in my preamble to Eric Olson’s profile); simplicity; an enduring passion for discovery and invention; and total commitment to the work.*

*Smithies’ statement that there is no substitute for hard work is one of the absolute truisms of life, as I elaborated last year in my preamble to Robert Lefkowitz’s profile. No matter how smart you are, if you don’t work hard, you will never make it. He is a living testimony of this concept. All of us should be astounded and inspired by the fact that this 85-year-old scientist, a Nobel laureate who has contributed so much to human knowledge, still works in the lab every day of the week, runs experiments, and exudes the same passion for science that he exuded 60 years ago. What a marvelous role model for young scientists.*

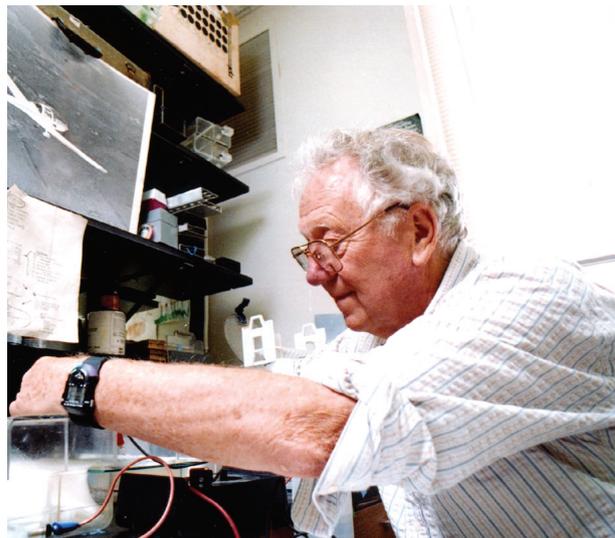
*Smithies has used wisely the talent that he was given. Isn’t that one of the most important things that we should be able to say about ourselves?*

—Roberto Bolli

In the 1980s, the work of Oliver Smithies, together with that of Mario Capecchi and Martin Evans, led to a whole new approach to studying mammalian genetics. These three scientists developed the necessary gene-targeting techniques that gave rise to knock-out mice.<sup>1–5</sup> They were awarded the Nobel Prize for their work in 2007.

Gene-targeting is a technique used by many modern molecular biologists. But a technique used by practically every molecular biologist, often several times a day, is running gels. Again, a large part of the thanks for developing this technique goes to Smithies who, in the 1950s, invented starch gel electrophoresis as a way to improve the resolution of the proteins he was studying.<sup>6,7</sup>

Smithies is now 85 years old and still targeting genes and running gels in his lab at the University of North Carolina in Chapel Hill—a long way from the town of Halifax in West Yorkshire, UK, where he grew up. Smithies stepped away from a spinning centrifuge—literally—to talk to *Circulation*



*Research about gels and genes and, also, about pigs’ bladders, car valves, blood pressure, and a lot more.*

### How Did You Get Interested in Science?

I didn’t really know what science was when I was a child. We didn’t have science in our curriculum in elementary school. So, my first exposure to it was through a comic strip that had an inventor as its leading character. I thought that seemed like a neat thing to be.

### What Was It About the Character That Appealed to You?

Well, like the character, I was definitely a tinkerer. I liked fixing things. In fact, there’s a photograph of me taken when I was just three or four, and I’ve got this wooden train and I’m lubricating the wheels with water from a bottle.

When I was a bit older, but still before I was 11, I had some books of my grandfather’s that were full of experiments you could do. One was to make a telephone. You had to start with a piece of wood and cut a hole in it, then get a pig’s bladder, and I mean literally a pig’s bladder from the butcher, and fasten it across the hole, and put a button in the middle, and attach a weight to stretch it into a cone—to make a loud-speaker. Then you attached a string to it and, at the other end, another cone. My friend and neighbor made the other cone, but our telephone didn’t work. Nobody told us that you had to have the string tight. We didn’t know!

### What Did Your Parents Do for a Living?

My mother taught English language and literature at the local technical college. In fact, she taught my father—she married her student!

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My father was an insurance salesman. This meant he had to have a car—a very rare thing in those days. He had this old two cylinder Jowett. It was always wearing out its valves, and my father would replace them. I remember helping—well that’s a bit of an uncertain term. I was about 7—but later the knowledge came in handy. <sup>1</sup>

When I was in Wisconsin as a Commonwealth Fellow, aged about 27, one summer out of the 2-year course you were expected to visit other parts of the states. They gave you some money, about \$500, so I bought an old car and went all the way across the states and up into Canada. At one point, the car’s valves burnt out, and I had to do a valve job on the side of the road with some tools I borrowed from a near-by garage.

### **How Did You Go from Pigs’ Bladders and Car Valves to Studying Medicine?**

That’s a bit of a mystery to me. When I was in my last year at grammar school, I was fortunate enough to get a scholarship to Oxford. I’m pretty sure the scholarship was given on the strength of my chemistry and physics studies, because I only had a few biology lessons—taken at the girls’ school down the road. But for some reason, that is still obscure in my mind, I thought I might like to do medicine. The Oxford professors were a bit surprised, but didn’t mind, so I started off as a medical student.

During my third year of study, Professor Sandy Ogston, who had been probably the most important person in selecting me to be accepted at Oxford, came back from his war duties—he had been helping to study the decomposition of poison gases. He gave a talk about the use of chemistry to solve biological problems, and I was absolutely fascinated. I decided not to finish the medical course and to do chemistry instead. I’m a med school drop out!

I joined the second-year chemistry degree course and then went on to do a PhD. After that, I felt completely comfortable with biological systems and completely comfortable with chemistry, and those two tools have been vital to me in all my later work.

### **What Drives You—Invention, or Scientific Discovery?**

Probably, a bit of both. The two things for which I can claim some sort of contribution are the invention of high-resolution gel electrophoresis in the 1950s and gene targeting in the 1980s.

The first one of those arose when I was in Toronto working in the laboratory of Dr. David A. Scott. He was an insulin specialist and told me I could work on anything I liked, as long as it had something to do with insulin. I decided to look for an insulin precursor. But in doing so, I was limited by the electrophoresis that we used at the time. The result was my development of starch gel electrophoresis. So, it was the need for the technique that caused its invention.

With gene targeting it was similar. I had been doing a lot of work on the fetal globin gene family, and it was known that a single base-pair mutation in the beta chain could cause sickle cell anemia. We had the normal genes in our test tubes, so I began to think there must be some way of using the normal DNA to correct the abnormal DNA—by some sort of

crossing over. Something like that had been done in yeast, but most people thought that it would be impossible in humans.

Again, I needed a method. I read a paper where the authors used a novel method, which I thought I might use to test whether gene targeting is possible. That paper came out on April 2, 1982, and on April 15, I wrote a page in my lab notebook describing how I’m going to do gene targeting in human cells. It took another 3 years to get it to work.

### **What Happened Next?**

Mario Capecchi was doing similar work, and the two of us approached Martin Evans to try the technique in mouse embryonic stem cells. It was too inefficient to be useful for therapy, which is what I was thinking of originally, so instead we thought about using it to alter genes in the mouse. That took another couple of years. Then, the three of us had to wait another 23 years for the Nobel Prize committee to recognize that this was important.

### **How Did You Become Interested in Blood Pressure Control?**

I happen to have hypertension and was using an ACE inhibitor to control it. I had been reading the literature on the genetics of hypertension when I had a visit from a medical resident named John Krege, here in North Carolina. He asked me if he could join the lab. I said, okay, what have you been working on? He said, preeclampsia, which he explained was hypertension that develops during pregnancy. I said, ooh, I think we could do something.

We made an ACE knockout mouse, which proved not to be terribly important. But, about a year later, a paper was published reporting a change in the angiotensinogen gene that the authors thought might be associated with risk for hypertension.

I thought, let’s make the same change in a mouse. It turned out that the mouse sequence was already different at that amino acid position, so you couldn’t do the experiment. However, this difference suggested that the amino acid change might not be important. The authors of the paper were themselves suspicious and thought that the level of the angiotensinogen protein in the plasma might instead be to blame, because people with higher blood pressure had higher plasma levels of the protein.

It wasn’t clear whether the high plasma angiotensinogen was a cause or effect of hypertension, however. So, I decided to alter the level of expression of the gene in mice, and that proved to be extremely successful and led to a whole change of my thinking toward the importance of gene expression levels.

### **And You’ve Stuck With the Subject Ever Since**

Yes, because, as I say when I’m giving talks, take a look around this room, no one has knockouts of anything, everybody—well nearly everybody—has ten fingers and two eyes and so on, but they vary in shape and length. Everybody has quantitative differences.

Small quantitative differences affecting a lot of genes are most likely to be the cause of blood pressure differences. Genes that have big effects on blood pressure are quite rare.

### What Advice Would You Give to Young Scientists?

Find something that you enjoy doing. Because most of the time, you are not going to be getting some stupendous result; you are going to be getting something that didn't work. So, for example if you are running gels, and at the end of the day they didn't show you what you wanted, at least you can say, "but it was a pretty gel."

It's good to have a big aim, but on the way to that marvelous goal, which you might never reach, if you've done a series of things that you enjoy and you keep publishing with those things, then you'll have a happy time, and you'll be productive.

### Anything Else?

There will be times when you're a bit fed up with your work—that's the single most common reason for people losing their interest in science—they get bored. There's a fairly simple solution, though it's not so simple in practice, and that is to do something different. It happened to me: the pages in my lab book, before I wrote that page on how to do gene targeting, are on experiments that were not working, and I didn't really like anymore. I didn't care about them.

So that's my other piece of advice—if you're feeling bored, change. It can be difficult, because if you change fields you certainly are not going to be funded right away. But, maybe you can collaborate with somebody who is in the field you are interested in and publish something with them. Don't be frightened of branching out.

### Other Keys to Success?

Work hard. There's no substitute. But then, you see, it isn't really work if you are doing something you enjoy. I still come back to the lab on Saturdays and Sundays and do experiments all the time.

I might work a little bit less than I used to, I might go for lunch with my wife or go flying, but I'm in the lab nearly every day, every week. In fact, I'm doing an experiment right now, my centrifuge is running. I did an experiment yesterday

morning, all of which failed because I'd made a mistake, and in the afternoon, I repeated them and got it right. So, I'm reaping the benefits—I hope—this morning.

### I Hope It Has Worked!

Yes, so do I. I'll find out in a few minutes.

### How Often Do You Go Flying?

Well I've been a pilot for more than 30 years. I learned rather late in life, and I've had a number of airplanes. They were all single-engine airplanes, typically Cessnas. I would fly myself to meetings and so on. At the same time, I developed a passion for gliding which I'd always wanted to do since childhood. I bought myself a motor glider, which can take off by itself, and then you turn the engine off, flatten the propeller, and use up-currents to fly. It's a fun machine. I try to fly it every weekend. Now, I only have the motor glider. I go by myself for an hour or two and you don't think about work or anything else. It's a full-time occupation and very enjoyable. I've been very fortunate to be able to keep flying for so long.

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