



Futures in Biotech, 45: How To Make A Mouse

Leo Laporte

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Marc Pelletier

This is Futures in Biotech, Episode 45: How To Make A Mouse, with Dr. Oliver Smithies

Leo Laporte

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[Music]

Marc Pelletier

Welcome to Futures in Biotech. I am Marc Pelletier. Today we are extremely fortunate; we have Dr. Oliver Smithies from the University of North Carolina at Chapel Hill School of Medicine and he's the 2007 Nobel Laureate in Medicine. He shared the prize with colleagues Mario Capecchi, and Sir Martin Evans for their discoveries of principles for introducing specific gene modification in mice by the use of embryonic stem cells. And let me just say that this is a paradigm shift in modern medicine. It enabled a revolution in genetics that allowed us to really bring mammals into the fold of molecular biology. So I'd like to welcome Dr. Smithies to Futures in Biotech, but I'd also like to thank you for welcoming us into your lab. So this is great, we're going live on video.

Dr. Oliver Smithies

Very good. Very good, Marc.

Marc Pelletier

What a privilege to join you in your lab. This is great. Thank you.

Dr. Oliver Smithies

Nice to have you in our place.

Marc Pelletier

I've heard that you spend quite a bit of time in the lab, it's...

Dr. Oliver Smithies

I was working this morning and this afternoon doing experiments still. I still do experiments.

Marc Pelletier

Is that bench right behind you yours? Is that the..?

Dr. Oliver Smithies

Yes, that's my bench, it's messy.

Marc Pelletier

Cool. So –

Dr. Oliver Smithies

The inside of my test tube is not messy but the outside is messy.

Marc Pelletier

That's okay. I think, you know, setting the standard is something that you do, so there's going to be a lot of scientist here watching and sort of modeling their work on yours. So all our benches now are going to be exactly like yours.

Dr. Oliver Smithies

I hope not.

Marc Pelletier

Let me ask you. When looking into, you know, Wikipedia, which – I apologize to the audience that I'm using Wikipedia for research here. But it said that you were the first to do gel electrophoresis and you developed that methodology. Is that accurate in Wikipedia?

Dr. Oliver Smithies

Oh yes, it is the first use, what we might call high resolution gel electrophoresis, that enable you to separate proteins and other substances according to molecular size. So it increased the resolution of electrophoresis very considerably and led to all sorts of new findings.

Marc Pelletier

Electrophoresis, for the audience here, is a technique that we do in molecular biology. Could you explain it a little bit?

Dr. Oliver Smithies

Yes, it's a fairly simple idea. If you imagine a solution of, say a salt solution, just salty water and you were to put a protein into the salty water, a mixture of proteins into the salty water, the proteins don't all have the same electrical charge; some of them have more positive and some have more negative. And so if you pass a current through that solution the proteins will move according to the charge. The more charged they are the faster they will go, and if they have opposite charges, they'll go in opposite directions. That's what electrophoresis is. That would be electrophoresis in free solution.

Now what I did – and in a way quite accidentally, and I can tell you about that if you like...

Marc Pelletier

Sure.

Dr. Oliver Smithies

...was to introduce the idea of doing this in a gel, for reasons I'm going to explain later. And it turned out that when I did this sort of separation, this electrophoresis in a gel, the – an added component came into the separation, because big molecules couldn't get through the gel as easily as small molecules. So now the – added on to the charge separation was a big influence of size that increased the power of the electrophoresis method very considerably. And it's used every day in – a modern molecular biology lab will use gel electrophoresis. It'll be, probably won't be the sort of gel I used which was starch gel. They'll use polyacrylamide gels now or they'll use agarose gels. But it's used all of the time. And if you open a scientific journal that's talking about molecular things, you find that more 50% of them will be using gel electrophoresis in one form or another.

Marc Pelletier

[6:20] Absolutely. I'd like to say to the audience that gel electrophoresis is somewhat like giving a molecular biologist – it's similar to giving a molecular biologist what is giving a telescope to an astronomer. Right, it allows us to separate the proteins and visualize them, or DNA, and even to such a resolution we can separate strands of DNA by one single base. So this absolutely revolutionized how everybody works in life sciences.

Dr. Oliver Smithies

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Of course – of course, Marc, all of those things didn't happen at the beginning. It was relatively simple...

Marc Pelletier

Right.

Dr. Oliver Smithies

...when it began. But it showed the differences in the proteins of blood, blood proteins, differences in different individuals. And so I became interested in genetics because I became interested then in what made some people have different size proteins than others and that it was inherited. And so I became a geneticist.

Marc Pelletier

And how long did it take before it really took off?

Dr. Oliver Smithies

It took off very –

Marc Pelletier

Electrophoresis as a technique.

Dr. Oliver Smithies

That type of electrophoresis took off very quickly because it was very obvious that it was a big improvement. And so my paper on electrophoresis was quoted many, many times in the scientific literature until people forgot. And they don't bother to quote anything anymore. Of course, they just use electrophoresis and that's fine. I'm happy about that.

Marc Pelletier

Is it the most quoted paper? Is it the highest – that must be the most quoted paper ever. Maybe perhaps Laemmli sample buffer.

Dr. Oliver Smithies

No, actually I have a paper on – in Computer Science which is, which is my most quoted, it's now more than 10,000 quote – citations, so.

Marc Pelletier

You know when I was first dating my wife, we were both in graduate school and she was doing – she was in molecular biology lab and she was running DNA sequences on – in gel electrophoresis. And my – for our first year of dating, all our dates happened within the two-hour span it would take to run a DNA gel. So I suppose that it's your fault.

Dr. Oliver Smithies

Yes that's right. I've destroyed many marriages.

Marc Pelletier

Yeah, God, I must have run thousands. And I think this is a really, really fun thing, for people to finally meet the person behind electrophoresis. Because as I said, everybody's doing it, every lab has ten boxes where they're separating proteins and DNA and other nucleic acids and it's just so much fun. So, you did this in 1950.

Dr. Oliver Smithies

Yes.

Marc Pelletier

So you've been – you've been – and that's when you decided to become a geneticist?

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Dr. Oliver Smithies

Yeah, when –

Marc Pelletier

I'd like to know – go ahead.

Dr. Oliver Smithies

Yeah, the reason was, basically, the observation was finding differences in the proteins of different individuals using the gel electrophoresis. And after a slightly abortive idea that the difference was due to whether you are a male or female, which turned out not to be true, the idea was fairly obvious that it might be a genetic difference. And then I got help then from a geneticist in Toronto where I lived and where I was working at the time. And she, Norma Ford Walker, and I worked out the genetics of this particular protein. And that made me in a sense become a geneticist, because I became very interested in then, in the things that made people different. and in the proteins and how they differ from one person to another.

Marc Pelletier

In that era, that 1950 to 1950, maybe 55, how did you view genetics? You knew that – did you know that the genes encoded the proteins, I suppose yes. But at what level of detail did we understand?

Dr. Oliver Smithies

[10:33] By then it was pretty clear that proteins were – the structure of proteins was dependent upon specific genes. For example, the blood groups were beginning to be very well understood. There were many different red cell blood groups and they were inherited relatively simply. And one protein had been worked on – one protein now was distinct from a red blood cell substance. One protein had been worked on and that was haemoglobin and it actually had been recognized first by Linus Pauling that there was a difference in the protein in people who had sickle cell anemia, haemoglobin being the protein. There was a difference in the haemoglobin of a person with sickle cell anemia compared to a person who doesn't have sickle cell anemia and that the heterozygote, that's to say the person who had one parent that had the normal haemoglobin and one that had the sickle cell haemoglobin, that individual would have both proteins so you could have either the normal haemoglobin or you could have the sickle cell haemoglobin or you could have both haemoglobin. And that it was determined by a simple genetic difference.

It's rather a interesting difference actually, because – and quite correctly, that sickle cell is a handicap. But actually to have one copy of that gene and one normal gene is extremely beneficial in certain circumstances and the circumstances are if you had malaria. And so in malaria areas it was an advantage to have one copy of the sickle cell gene and one of the more common, normal gene. You would survive better than the person with two normal genes and that's why the frequency of that gene increased very much in populations that were exposed to malaria.

And of course then, my proteins I began to think – I call them my proteins, they weren't mine, but the proteins that I was studying, it seemed very clear that they might have a genetic basis and that's what Norma Ford Walker and I worked out. And later on, then we went on to work out what the actual difference in the proteins was. And that led to what I later did too. So it's usually a long sequence of events, as usual science is, one thing leads to another, to another and so on.

Marc Pelletier

An amazing journey. The – I'd like to know, you know, I rarely get the chance to speak to someone who started as a geneticist in 1950 and is working today in 2009. You've see a major revolution in life sciences, right? And this – I'd like to know a little bit about those transitions from when the structure of DNA came about, to the understanding of gene structure. If you tell us a

little bit about some of the experiments that really excited you during those early decades, it'd be really, really fascinating.

Dr. Oliver Smithies

I'll try. As a matter of fact, you mentioned where it began from the year, which is when it was first discovered that DNA was the genetic material. Well you see that was not known. People didn't really know what the genetic material was. They thought it might be protein, because proteins were complicated. Nobody had thought it would be DNA, which is a relatively, chemically rather simple substance and they didn't it was that. But I remember my professor of biochemistry when I was a student – I was a medical student at the time, coming in to the classroom, sort of shaking his hands around, being excited and saying 'it's just been discovered that DNA is the genetic material' and that was discovered in New York by MacLeod, McCarthy and somebody I can't remember the, third, name of. I know it really, but old age, you know, you forget names. But...

Marc Pelletier

Virologist?

Dr. Oliver Smithies

That was the beginning, that was when DNA was found to be the genetic material and then in the sense that the work with the haemoglobins was the beginning of understanding that the genetic differences could be seen, could be reflected in proteins. And that was the work that was going in the late '50s and early '60s and then people learned how to sequence, how to determine the structure of proteins. Fred Sanger invented that technique and he got the Nobel Prize for that.

And then Fred Sanger again invented the procedure for sequencing DNA and Wally Gilbert at the same time, Wally Gilbert and Maxim and Fred Sanger invented methods for determining DNA sequence and that was a huge step forward and the other investigators learned, in between the protein and the DNA sequencing, learned how to isolate particular pieces of DNA, that's called cloning DNA, where you could isolate a particular piece of DNA and get many, many pure copies of it. And actually it was that business that led me to do the work for which the Nobel Prize was given because I knew about the mistake in haemoglobin, as it were, mistake is perhaps the wrong word, but the difference in sickle cell haemoglobin from a normal haemoglobin. And we – I knew that difference and we already had DNA available cloned from human individuals that had normal haemoglobin gene and had the altered haemoglobin gene and my dream was then to take the piece of the normal DNA, as it were and introduce it into a cell and that it would then cure the abnormal haemoglobin. That was what I set out to do you see.

Marc Pelletier

Gene therapy?

Dr. Oliver Smithies

Yeah, I was thinking about gene therapy, correcting a gene, that was my initial aim and that was back in 19... oh probably in 1982, something like that.

Marc Pelletier

1982.

Dr. Oliver Smithies

In fact it was 1982.

Marc Pelletier

Wow. And so what was your approach. How did you go about introducing it into mammalian cells?

Dr. Oliver Smithies

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Well, I didn't, I had been dreaming about, I mean off and on thinking about it and other people had been thinking about it, but most people thought it wouldn't work with humans. It had been shown with yeast, which is much less complicated organism than the human individual or a mouse for that matter, that if you did introduce DNA into a yeast cell it would modify the corresponding or could modify the corresponding gene.

So that was known and I thought that I wanted to try it with a human situation or with mammalian situation, but the mammalian genetic material is a hundred times more complicated than mouse and most people I think thought it wouldn't be possible, but I was teaching a class at the time and I read a paper that used a technique, describes a technique for isolating rather rare pieces of DNA and I thought maybe I could modify that technique to let me determine whether I could alter a gene.

So I had this idea that using this technique with the obvious changes, I say obvious changes, I mean it wasn't exactly that technique, it was that technique with other things added to it, that I could test whether I could alter a gene in a living cell, a living mammalian cell, a complicated cell. So that's what I set out to do in 1982. It took three years before it worked. But that's not unusual in science, you have to be patient.

Marc Pelletier

Sure, and determined as well.

Dr. Oliver Smithies

Well, determined I suppose, but if you're doing what you like, there is nothing determined about it, you are just doing what you like anyway.

Marc Pelletier

I think it was 1982 that the movie Blade Runner came out from Ridley Scott, starring Harrison Ford and in that movie...

Dr. Oliver Smithies

Is that right?

Marc Pelletier

Yeah, and it was about the future of genetic engineering and I'm wondering, did they consult you?

Dr. Oliver Smithies

No, not me, they never consulted me about a movie.

Marc Pelletier

But they got the science right. So I am wondering if there's a connection here. Yes, because what you were trying to do was actually in the theatres as a sci-fi and it was very, very, very exciting. It's as exciting as it can possibly be. This is the first rounds of genetically engineering a mammalian cell, and for the audience, we're mammals, so to be able to start going from genetic engineering of viruses and bacteria and simple organisms like yeast and maybe fruit flies, taking it to the next level is outstanding. And so you were taking about changing a mammalian cell line but you know you can introduce a gene just randomly and throw some DNA in and the cells will take it up. But that wasn't your idea, to just throw a gene into a cell?

Dr. Oliver Smithies

You're correct, Marc. You see we knew, I knew, other scientists obviously knew that you could introduce DNA into a cell, but the DNA integrate into the cell – the genetic material of the cell but it would go anywhere. So it was random. My idea was to put the DNA in a known place so that I could alter a known gene rather than just randomly and that was what I was trying to do and eventually succeeded in doing.

Marc Pelletier

And how does one do it? How does one throw in a gene to a specific place?

Dr. Oliver Smithies

[21:44] Well it's still a little bit of a mystery in a way. What you do is you take a piece of DNA that covers the area of the genome, the genetic material that you are interested in, you introduce it into a cell. In our particular way you can introduce it by punching holes in the cell with an electrical shock and that lets your DNA into the cell without killing it if you get the thing, just adjust it correctly. And then this DNA seems to find its partner. Doesn't do it very frequently but it will eventually find the right place to interact with and then occasionally they exchange partners so the piece you put in replaces the corresponding segment that was in the cell at the beginning. You can think of it as like, imagine that you have a book except in the case of genetic material you have to have many, many books, a thousand books. You have a thousand books and there's one sentence in there where there's a word wrong and you would like to change it. And so you take the rest of the – you take that same sentence, correct sentence now and you introduce the correct sentence into this mixture of a thousand books and then by this magical process it finds the right place and occasionally the exchange occurs. It's rather rare. I mean it's maybe once in a million cells will this happen. That sort of frequency.

Marc Pelletier

So it's like if you are editing a large manuscript and you throw it up in the air and then you throw a corrected sentence or a corrected page, throw into the middle, and if it lands on the right place, the same page where it was with just those subtle changes, boom.

Dr. Oliver Smithies

Yeah, but you could see that it wouldn't happen very often, would it?

Marc Pelletier

No, you'd have to throw it a million times into the air.

Dr. Oliver Smithies

Yes, that's right.

Marc Pelletier

But it was interesting that you said you have a word that needs correction, you'd replace it with an entire sentence. How did you know that you need an entire sentence to replace a word?

Dr. Oliver Smithies

Well it was pretty obvious that if you try to correct something with the word, let's say you wanted to change "this is a gene" to "this is not a gene". If you use "this is" as your searching sentence, it would find many, many places and so it wouldn't work. So you'd have to use a longer sentence as it were to get to the right place. That's the easiest way to think of it.

Marc Pelletier

Well how long did you – okay so let's now talk in terms of bases of DNA, how long in your first recombination experiments, how long did you start with? Did you start with 2,000 bases or did you start with 500?

Dr. Oliver Smithies

No actually started with, if I remember rightly, I had a thing called, that I called Cossos 17 [ph]; I think it was about 30,000 base pairs long.

Marc Pelletier

Wow!

Dr. Oliver Smithies

It's pretty – maybe it was a bit smaller, maybe 20,000. But we never really got that one to work and I made a shorter one that was about – something like, maybe about 5,000 bases long and that worked.

Marc Pelletier

5,000, all right, so that's really exciting. And then these were just cell lines right, that you initially did your recombination work in?

Dr. Oliver Smithies

Yes, well, then you see, I published that this was possible. But it was also – what had been shown really was that it was possible not that it was practical. You see, it was – the frequency of getting successful, of getting this to work was much too low to be valuable for therapeutics. So, the idea of using it for gene therapy is still a dream. I think that dream will one day be realized but it was pretty clear that the sort of thing that I was trying wouldn't be useful because it'd only work one in a million times.

But then what can we use this for and then we heard about the work of Martin Evans, Sir Martin Evans and his work with these marvelous cells which most people have heard about, embryonic stem cell. And he had shown with his students and his post-docs, he had shown that these cells which are derived from an embryo and can be grown in the laboratory in a dish, that these cells can be reintroduced into an embryo and when they get back into the embryo they remember, as it were, where they came from and become part of the final mouse, if you are doing it with a mouse. And so the mouse is now a mixture of the cells that you introduced, the embryonic stem cells plus its own cells.

In that way, Martin Evans and his collaborators showed that you could therefore – you could make a mouse from the cells that you had in a dish and I had the idea then of course why don't I try to alter these cells with this gene targeting as we now called the method. I could use gene targeting to alter a gene in the mouse cell and then make a mouse with the altered gene.

Marc Pelletier

This is a paradigm shift; you made a mouse, right?

Dr. Oliver Smithies

Yes, that's right. Now, we took a – and Mario Capecchi had the same idea at the same time because we both went in our various ways to Martin Evans. And it turns out that we were only three weeks difference in time in going to talk to Martin Evans to ask him for help. And he's a marvelous scientist and a generous person and of course he helped. And...

Marc Pelletier

Was there collaboration with you and Dr. Capecchi?

Dr. Oliver Smithies

Well, actually – we, he and Martin Evans and I never ended up by having a collaboration because the cells that he gave me weren't the ones that we eventually used, but Mario Capecchi did have a collaboration with Martin Evans because he did use the cells that Martin Evans had made.

Marc Pelletier

Before we go on in this area I would like to ask you a question, I am sorry, we do have about a half a second lag here, so there's a – sometimes it's difficult to – this whole interview process is sometimes difficult.

It's like the sound is actually going around the moon and back. So...

Dr. Oliver Smithies

Right.

Marc Pelletier

So, here's an amazing thing. You now can create a mammalian organism which – or to make one and the term make is not loosely used; it's very, very specifically used. You have engineered it to have specific genes and/or to replace a defective gene or a good gene with a defective one and vice versa. But so you were really hoping to get gene therapy with your method of introducing DNA into mammalian cells. Were you disappointed after three years that the – that it was difficult to do and would not fit the model for gene therapy?

Dr. Oliver Smithies

[29:35] No, not really. I think when you're a practical scientist, you know that the dream you have may be a long time before it can be made into reality and the fact that it isn't possible now is just a challenge, rather than something to make you unhappy about, something interesting still to do. I think that particular problem will be – I won't solve that one because I'm not working on that particular type of work anymore so some – the next generation will do it, I'm sure.

Marc Pelletier

Well I'd just like to say that both the recombination technique of introducing a gene to swap one out is the method that I've used to, found this company here that I'm working at. And the information that we used – the premise for the company was based on a mouse that had been genetically engineered to remove a gene and so the function of the gene, so we now understand molecular pathology of the problem. We know – I'm working on brain swelling, so we know where the – what gene can be disrupted and lead to an effective cure.

So now we're developing drugs to target that – the functional protein that comes from that gene. And it's all based on these technologies so to really put into perspective, it's quite amazing; one I'm using technologies to – in cell culture where I've replaced genes, specifically engineer my generic cells to have a human protein and it's based on the premise that I've knocked out a genes in the mouse that's similar to the human gene and that's elucidated the molecular mechanism of that problem.

So it's extremely powerful. Everything in the world of life sciences, in terms of pharmacology and molecular medicine is based on these two approaches which is a lot of fun.

So you first got embryonic stem cells in the lab, this is back in 1983 or '85, about?

Dr. Oliver Smithies

Let's see - I think it was a bit later than that, it was probably – maybe about '87 or something like that – '85 maybe I don't remember exactly when but perhaps '87, that sort of period of time.

Marc Pelletier

And how many people were working on these besides – was Dr. Evans the only person really being able to culture these because they're difficult to play with even today.

Dr. Oliver Smithies

Well no, Gail Martin who had been – I think a post-doc of Martin Evans, had also isolated embryonic stem cells. But I think she was rather pessimistic about their use and so never quite demonstrated their great potential whereas Martin Evans and his collaborators did, but the work – but Gail Martin was also in – doing that work at that time but as soon as Martin Evans – it was Martin Evans and Matthew Kaufman as soon as they published their work, many people all over the world began to be interested in using and working with them. So, as usual something exciting comes into science and many people will try.

Marc Pelletier

So this is the key to mammalian engineering, using embryonic stem cells and using the gene targeting to get your gene in the right place and to replace a gene or to add a gene – or to disrupt or to add a – to replace it. Disrupt it or replace it – I guess that's the best, best way to put it. What was the first round of experiments that you wanted to do, if you could create a mouse? So when you said; I think I can create a mouse with the specific genetics. What was the first experiment?

Dr. Oliver Smithies

I'm remembering back – I think the first experiment we did was with one of my poor post-docs at the time Beverly Koller and she came to the lab, she heard about the work that we'd been doing and she sent me a message and I don't remember whether it was a telephone call or a letter or what. But she said that I would like to come and work on one particular protein that she had been working with and the protein was called beta-2 microglobulin and I said, oh well, you know, Bev, I was the first person to do an amino acid sequence on that protein a long time ago. So by all means come and so she came and we began to work on beta-2 microglobulin. But then shortly after that the gene for – responsible for cystic fibrosis was identified and cloned and we thought it would be a good thing to try to make a model of cystic fibrosis.

Marc Pelletier

Was that the first genetic model of a human disease, in a mammal? The cystic fibrosis gene in the...

Dr. Oliver Smithies

Yes, I think in fact it was the first one of a disease, yeah.

Marc Pelletier

And so the...

Dr. Oliver Smithies

I was – excuse me – I was rather glad to have done it because I remember when I was – you remember I talked about Norma Ford Walker in Toronto the geneticist I went to, she had some families that were – that had children or babies or young children with cystic fibrosis and there was nothing you could do to help those children, or not very much, and so making a model of the – of that disease in a mouse was in a way very gratifying because it was like saying, well here's something to help those children that we couldn't help 20 or 30 years earlier.

Marc Pelletier

And so, being – that this is a great example I think CF – the CF mouse in that it now gives – you can breed those mice, right?

Dr. Oliver Smithies

Yes.

Marc Pelletier

You don't have to keep engineering them, you've got – you've got a litter of mice and you breed them within each other until they have the pure human defective gene and then you propagate them and pass them on to the world so everybody can start seeing if there is something they can do to alleviate symptoms or even find a cure.

Dr. Oliver Smithies

Yeah.

Marc Pelletier

So it's a great use – I guess it's not like the use of in Tyrell, the company Tyrell in Blade Runner where they, you know, create alien, or sort of genetically engineered humans to serve us. It's far more important. I digress. It's kind of my motivation to become a geneticist, life scientist, was that movie because it was so fantastic and here we are getting the real story of the actual initiation of this era of modern genetics. So I'd like to talk to you a little bit about some of the models – some of these mouse models of disease that you've enjoyed or that you have created and enjoyed working with, is there a – do you have a favorite mouse or you know perhaps we should do this chronologically, you know sort of like music, there's a chronologically way to categorize things and you can do it by favorites?

Dr. Oliver Smithies

Well, I – my wife made an extremely important model fairly early in this – in the area of making animal models and she did this completely independently of me, she use the method that I had worked with but she is an independent investigator and she made a mouse that would develop atherosclerosis, the fatty deposits in arteries and so on. And I thought that this was very neat because that's a very common condition, I mean it's common enough that maybe something close to 50% of those of us who are alive now will someday or rather have some intersection with atherosclerosis and many of us will die of heart attack as a result of it, so when she made a model of atherosclerosis she was dealing a disease that was a hundred times more common than cystic fibrosis.

Marc Pelletier

It's the number one human killer. Isn't it?

Dr. Oliver Smithies

Yes, exactly, the number one, maybe cancer might beat it, but it's pretty close. And so she made a model of that and I thought that I would like to do something with a common gene too and I began to think about making changes in genes that would affect blood pressure because having high blood pressure is pretty common too, maybe 20% of people, 15-20% of individuals will have some form of high blood pressure and that's why...

Marc Pelletier

15%.

Dr. Oliver Smithies

I made a lot of, well I say "I" – we made a lot of models of different – with different changes that would alter blood pressure: sometimes put it up, sometimes put it down. And we learned a lot about what genes affect blood pressure. That went on for maybe 10 years, maybe more time doing that type of model.

Marc Pelletier

Did you begin working together – I suppose, I don't know how to formulate this kind of question. Did you meet while working together? So was it the science that attracted you to each other?

Dr. Oliver Smithies

It was the science that brought us together. The attraction was nothing to do with science.

Marc Pelletier

All right. Well it can, it can. You know.

Dr. Oliver Smithies

That's just ordinary biology. But it actually was rather entertaining because we always say that Ronald Reagan was responsible for us getting together, because my wife was going to go to work at the National Institute of Health and Ronald Reagan froze all appointments because of some

budget crisis and wasn't going to let anybody work there and so then she came to work with me and then I – of course then the attractive element came in.

Marc Pelletier

Right. Fantastic. Well, so and you share space at University of North Carolina.

Dr. Oliver Smithies

Oh yes, we do. We've shared space here for 20 years, more than 20 years. It's very, very enjoyable but because we help lighten each other's loads as it were of making things work and we share joint equipment and we have many of our technical staff that are – don't think of themselves as either one, working either one or the other. Just working with us altogether. And her project are different from my projects, so we had plenty of independence but we have lots of – in common as well.

Marc Pelletier

And I guess as somebody who's been married for 12 years here, I understand that sometimes there can be disagreements, but your disagreements become professional as well sometimes.

Dr. Oliver Smithies

Well, I think the disagreements, the professional ones are more common than any other.

Marc Pelletier

Oh for sure.

Dr. Oliver Smithies

We argue about science very often.

Marc Pelletier

I would like to ask you a little bit about some of the techniques that – you know I was speaking to somebody who works in your lab yesterday in preparation for the show. He mentioned that you really, you were fond of PCR and I can imagine right in the early stages of your work, in engineering these mammalian cells, PCR would have been extremely useful to make those constructs. When it happened, how did you go about getting started on PCR – Polymerase Chain Reaction.

Dr. Oliver Smithies

[42:38] It happened in the way that lots of scientific things happen. I went to a scientific meeting and I heard Kary Mullis, the inventor of PCR, talk about the procedure. And – so I knew about it. And then sometime later when something clicked, as it were, in one's mind to say that I could use PCR as an easier way of finding out if my gene had gone into the right place in the experiments of gene targeting. And so you couldn't buy any apparatus for PCR. Nothing was on sale at that time. It was too early, nobody had manufactured any equipment and even the enzymes that were used, you couldn't buy. And so eventually I just made a machine with a person in my lab, Hyun Sup Kim [ph] and I made the machine with our lab technician together, Jose Fabolder. I remember his name very well. Jose Fabolder made the equipment and with my design and Kim did a lot of the early testing and we made it work.

Marc Pelletier

It's amazing technique because it allows you to amplify –

Dr. Oliver Smithies

I still have the machine that we made, which we – and I use it. It's a cumbersome machine to look at, but it does a real good job. I can beat anyone in the lab on PCR.

Marc Pelletier

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So you still use it? You still use it?

Dr. Oliver Smithies

Oh yeah.

Marc Pelletier

Somebody said there was some cattle prods involved.

Dr. Oliver Smithies

Some what?

Marc Pelletier

Cattle prods, to heat the water, to heat the baths?

Dr. Oliver Smithies

Oh yeah the – I think I know what are you're talking about. The big water bath. Yeah. It had three big water baths originally. So there were two tubes went in each water bath. So if you think that there were three water baths and there were six tubes and they looked like tentacles. So we call it a hexopus. Hex being six of course and hexopus, so that it wasn't an octopus, it was a hexopus.

Marc Pelletier

Hexopus yeah. So that people get an understanding here, some people will know what PCR is. Others – it's when you take small segments of DNA that match a region and so if you've – trying to find out whether if you've introduced a gene into the specific spot, you know what the genes, the region looks like, you can make little small segments that match that area and then start photocopying just that area. Then once you amplify it, then you run it on a gel, using gel electrophoresis, another methodology that Dr. Smithies started off, and resolve the length of that. And because you know exactly where you're amplifying from, you know exactly how long that DNA is supposed to be. So you can tell whether or not your gene's integrated into the region of interest and I suppose it's fun too if you're trying to clone and take pieces of DNA out of the genome and play with them. It gives you so many copies that you get to – and you've got enough material to actually physically work with. And if you spill it on your bench and your bench is clean, I guess you can pipette it back, right? Back up.

Dr. Oliver Smithies

Yes.

Marc Pelletier

It's a good reason to keep a bench clean I suppose. I used to keep my bench, my lab bench so shiny that I could see my face on it. Because I was a sloppy scientist I would spill.

Dr. Oliver Smithies

Well I am afraid mine is not so tidy as that and I'm still a bit of a sloppy scientist. So there's a bit of a problem as you can see.

Marc Pelletier

Yeah. Well I really, really appreciate you coming on. Before we go, I'd like to ask you a little bit about your hobbies. I know that you spend a tremendous amount of time in the lab and – but when you're out of the lab, what do you like to do?

Dr. Oliver Smithies

Well my hobby's flying still. I still fly an airplane, a motor glider really and it's a nice machine because you can take it off and you can turn the engine off and you could look for an up current underneath a cloud and sail around and go – if you're fortunate, you can go up, if you're not so

fortunate, you come down and then you can – of course you arrange it so that you come down where there's an airport. So it's not that difficult. But that's just my hobby, flying.

Marc Pelletier

Do you find that it's productive at helping you find ideas?

Dr. Oliver Smithies

Oh, no. When I'm flying I am not thinking about science. When you're thinking about – you shouldn't be thinking about anything other than flying if you're flying.

Marc Pelletier

Keep your eye on the ball, great. Well that sounds like fun. And how did you pass your exam? It said on – in some of the – my research here, that you're color blind.

Dr. Oliver Smithies

Well it turns out that for a glider license you don't need to pass any medical exam. That's one thing. So for my motor glider I don't need a medical license. I just have to be fit, you might say. For a regular license I had to pass medical exams as everybody else does, but because I'm color blind then I have some restrictions and the restrictions are that you can't fly at night, because you can't tell the colored lights that you use at night reliably.

And it's obviously important to know whether green is on the left and red is on the right, if that's the case whether it's coming towards you or if the opposite way around it might be going away from you and vice versa. And you have to know which the colors are. But since I don't know the colors anyway I never learnt whether the green was on the left or red was on the left. I didn't have to. I never flew with lights.

Marc Pelletier

And I guess there's not too many wind currents at night. So, it won't be too productive to use a sail plane at night.

Dr. Oliver Smithies

Yeah, no, sail planes don't work very well at night. There's no up-current at night, or very little anyway in the usual way. Unless you're in a thunderstorm. And you don't particularly want to be in a thundercloud with a glider. Although some people used to do that. Oh yeah.

Marc Pelletier

Yeah, extreme sports. It is an extreme sport, definitely an extreme sport.

Dr. Oliver Smithies

Yeah, an extreme sport that. They would often come out of the cloud with a parachute.

Marc Pelletier

Do you carry one in your glider?

Dr. Oliver Smithies

No. no.

Marc Pelletier

Well I guess the plane itself is like a parachute.

Dr. Oliver Smithies

It's very safe.

Marc Pelletier

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Yeah. Well hey, I'd very much like to thank you for coming on the show. This is a huge privilege for me as a scientist and a host for a tech show to have someone who's made so many changes and revolutionized science. It's not evolution, but revolutionized science. So thank you very much for inviting us into your lab.

Dr. Oliver Smithies

It's been my pleasure to have you here.

Marc Pelletier

I'd really like to thank Dr. Oliver Smithies who is a professor at the University of North Carolina at Chapel Hill School of Medicine and 2007 Nobel Laureate in Physiology and Medicine – or Medicine. And I'd also thank John Kavik [ph] and Jenny Hall [ph] for helping me set up the interview over at the University at North Carolina. I would like to thank Colleen Kelly, our new producer of Futures in Biotech and Eric Flanagan [ph] for working the boards; and Leo Laporte and Dane Golden for helping make this possible.

I'd also like to thank the fellows at Pods in Print. So, transcripts are available for this show and you can get them at futuresinbiotech.com. So, if you need transcripts done, these guys can handle very technical material as they do with Futures in Biotech. So if you need transcripts or you'd like to get the transcripts to this show, go to podsinprint.com and futuresinbiotech.com.

Lastly, I'd like to thank Phil Pelletier and Will Hall for the opening and closing themes.

For Futures in Biotech, I'm Marc Pelletier.