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An Interview with Dr. Derrick Rossi, Co-Founder of Moderna Therapeutics

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In 2012, Dr. Rossi was the inaugural New Investigators Invited Speaker at the 41st Annual Scientific Meeting of ISEH. He generously agreed to be interviewed by a member of the New Investigator Committee about his captivating career path and successes in translating discoveries to the clinic.

Among Dr. Rossi's numerous accomplishments, we can list the development of an approach to generate induced pluripotent stem cells (IPSCs) using synthetic modified messenger RNA, which was named by Time magazine as one of the top ten medical breakthroughs of 2010. Dr. Rossi leveraged that technology

to found Moderna Therapeutics, which is now a major supplier of vaccines against COVID-19. In 2015, Dr. Rossi co-founded Intellia Therapeutics, a publicly traded Cambridge-based company focused on developing CRISPR/Cas9-based therapeutics. In 2016, he co-founded Magenta Therapeutics, which is focused on transforming hematopoietic stem cell transplantation. In 2017, he helped launch Convelo Therapeutics, which is developing remyelination therapies for patients suffering from neurological diseases such as multiple sclerosis. Until recently, Dr. Rossi was an Associate Professor in the Department of Stem Cell and Regenerative Biology at Harvard Medical School, principal faculty at the Harvard Stem Cell Institute, Robertson Investigator of the New York Stem Cell Foundation, and investigator in the Program of Cellular and Molecular Medicine, Children's Hospital Boston. He currently serves as the founding CEO of Convelo Therapeutics.

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Could you talk to us about some key events in your training that helped you develop your successful career?

I actually took a very non-linear path through my career in science, which is different from most people. I started a PhD program in Toronto, which I did not complete because I moved to Paris, France. I was in yet another PhD program there, which I did not complete, and then I moved to Texas. My third PhD program was in Helsinki and that one I actually got. Along the way, though, I did a lot of science. I worked on early embryonic development to gastrointestinal polyposis, to peripheral myelination, so I got to view this really broad swath of biology and molecular biology.

So, although I ended up doing my postdoc and getting my faculty position later in life compared to most people, I would argue that it gave me a real big perspective on biology, and which I would not trade for anything. I really feel that it was important for me when I eventually became a full-time scientist. That is an

unusual career path that most do not take, although I have mentored people to take things slowly if they possibly can. There is plenty of time to be an adult later in life but being a young person - getting as much exposure and becoming a well-rounded individual – is really important for one's later career as an adult. It can give you some creativity and some perspective that those that follow the real fast track do not have.

Can you describe some of the mentors that motivated you during your training?

There were many. Dating back to my original graduate program in Toronto, Alan Bernstein, with whom I am in contact now about Canada's response to the COVID pandemic. Then I worked with Gilles Thomas and Olivier Delattre in Paris - they were geneticists who were taking their genetic findings and researching the biochemistry and molecular biology. Then I worked with Tomi Mäkelä in Helsinki - he had just come out of Robert Weinberg's lab and started his own lab, so he was a real rising young star and smart guy. I decided to go work with Irving Weissman because I wanted to focus on stem cell biology and the intersection with aging. Irving is well known to the ISEH community – he is brilliant, and he was a great mentor to me. Even when you start your faculty career, you still need mentors, so when I got to Harvard, Fred Alt was my Department chair - a great scientist, a great friend, and mentor to me - as was Doug Melton. So, you always need mentors, no matter what state of your career you are at, and they can really help you think about getting it right.

In retrospect, what kind of skills did you acquire that you think were the most useful to your career as a scientist?

I would argue that if there is already somebody in your community who has perfected the round wheel for the scientific direction that you want to go in, you should collaborate with that person - reach out and be really open about your science and get experts involved. That is how I approached things even as a post-doc. I remember approaching my fellow post-docs - Irving Weissman had a huge lab - and when I had something that I wanted to do and there was somebody else in the community that was really good at it already, I would immediately reach out to them and start to collaborate with them. So, the message is: often in the settings that we are at these universities and teaching hospitals around the planet, there are some really great people that already are experts in some aspect of what you want to do, so you should always be open with your science and reach out for collaboration because that is the best way to move science forward.

Can you describe to us your first contact with ISEH and how it played a role in your career?

The annual meeting was my favorite meeting every year, because it is really focused on hematology and

hematopoietic stem cell biology in particular. So, it is a meeting that I really enjoyed going to every year. It is the one that was really focused on what I was interested regarding hematopoietic stem cell biology. At some point, ISEH reached out to me and offered me an opportunity to speak at the annual meeting as a new investigator and it was a great honor. I have been a member of ISSCR too because sometimes it is really important to get outside of your box and learn some ideas that are in totally different fields, and then be inspired to apply them to your work. For example, Yamanaka's work, which I first saw just prior to his publication in 2006, was so fantastic. I loved the science and then we were inspired by that in my lab: we did a number of projects using multi-transcription factor approaches, trying to reprogram blood cells back to HSCs, but also our efforts in generating integration-free IPS cells led to this modified mRNA technology that people are now getting in their arms.

Do you have any advice for people who are starting their own lab in regard to what kind of projects they should take on at first?

Well [laughs] this is probably not good advice, but this is what I did. Often, you write your grants or a sort of proposal when you are starting your lab, where you lay out your first five years, and I think it is a terrible idea to stick to that plan. Of course, the discoveries that you will make in year one and two will inform where you go in years three, four, five, and so on. So, I think a long-term plan is quite silly actually because it makes no sense scientifically. My advice is to really go where your interest lies, go where you are passionate, and do not go where your grants said that you were supposed to go. I know that you are supposed to do what you said you were going to do, but I never did that. I always had a pool of money from many different grants and funding agencies and then we just followed whatever science was interesting and wherever the data led us. And honestly, write the grants - you have to do it, unfortunately - but I do not think that you should stick by that road map. Where the data and the passion lead you is where you should go.

When you started your own lab, did you already have the plan to translate discoveries from the academic lab into start-up companies and then to the clinic?

I did not. I had, like many young people, a career in academia as my focus - it is one of the best jobs you could imagine. I had seen translation from the lab to biotech from my time in Irving Weissman’s lab because he had translated several ideas out of his lab to biotech start-ups that ended up in the clinic. Sometimes, he did not even do it via the biotech route but rather just ran investigator-led clinical trials from his lab and from collaborator labs. So, I was interested in that and got my first real good look at it when I was at Stanford during my postdoc. As you know, I was working on hematopoietic stem cell aging and I thought that there might be an opportunity to move something. But, in all the time that we worked on it in my lab, not once did I start an aging company.

So, the first real experience I had of doing it myself was with modified RNA and the work, inspired by Yamanaka's work, where we were trying to make integration-free IPS cells, which is very important for moving those cells to the clinic. There was a lot of different labs working on different strategies and a project led by a postdoc in the lab at the time, Luigi Warren, had this idea to use mRNA to generate integration-free IPS cells. There was a lot of work that we did over years that led to this modified mRNA concept, which was really required to do this. Then, it was funny that, as we were getting ready to publish our paper - word was getting out because it was an exciting story at the time – all these pharma representatives were calling me saying: "Hey, we would really like to license that IPSC technology from you". Pharma was trying to use IPSC disease modeling in their labs, but I was surprised that nobody in any of those calls recognized that the modified mRNA technology itself, the ability to express any protein that one wanted, to me that was the important thing. And if you could translate that in vivo, now all of a sudden you had an ability to do gene therapy without the genes, without the DNA. We demonstrated that you could use this technology temporally, it was dose dependent, you could repeat a dose if you needed to - so many properties of it made it really exciting for a possible therapeutic translation. So, that is on what I founded Moderna - the idea of translating this technology towards therapy.

It is funny because Moderna was in stealth mode for many years and people just thought we were working on IPS cells or something like that, but there was not a single experiment ever done on this. It was all about turning this modified mRNA into a therapeutic itself, which you know now 10 years later has borne fruit with this COVID vaccine, for example.

Did you have specific diseases in mind as you founded Moderna?

Not a particular one because part of the challenge with such a technology was an abundance of riches - you could work on so many different things. Human disease almost invariably comes back to some sort of mis-expressed protein or misfolded protein or some other aspect of protein biology - 6000 genetic diseases. I was trained in molecular genetics, so I was thinking about genetic diseases. On the other hand, this is a new technology and mRNA is a macro molecule, so you have to think about efficient delivery. The good news for us was that small interfering RNA technology had been developed about 15 years prior and they had already gone through the challenge of delivering much smaller siRNA, but the concept was there – by lipid nanoparticles, for example. It turns out that we did experiments in the lab where you could even put in unprotected mRNA - not in a vehicle - and get expression, which is pretty amazing. So really, it was "what can we work on?", and I will say that that vaccines were not high on the list at the time, although it is a perfect application for the technology. You have to get one dose to a patient who has never seen an antigen before and you can noninvasively measure their peripheral blood to see if they have responded to it, to see whether or not it is safe and effective, and you can do it intramuscularly. So, it is a very good application, and indeed how Moderna ended up getting into it some years ago, well

before COVID.

Thinking about genetic disease primarily, we did a couple of proof-of-concept studies in my lab, that were actually never published, to see if we could have some sort of therapeutic outcome. I remember some experiments that were done in my lab by Pankaj Mandal, Wataru Ebina, and Morag Stewart, where we made human erythropoetin – and for which there is an ELISA essay that distinguishes between mouse and human. We made the human EPO mRNA, we injected it into the thigh muscle of the mouse, and sure enough the red cell counts went up in a dose-dependent manner. So, it told us that we could put a human gene, or basically a modified mRNA for a human protein, into mice. By the way, this worked on the first time we ever did it - that tells you something about the robustness of the technology. We did that in 2010 or early 2011. We also made luciferase and again the first time we did it - experiments done by Lior Zangi and Pankaj Mandal - we saw dose-dependent luciferase expression in the thigh muscle. Then we also went into the heart, the lung - we started exploring different tissues with various collaborators and every time we went into a different issue, we got expression of modified RNA. I had just founded Moderna at the time and these were the key experiments.

Prior to that, the study that was published in Cell Stem Cell was all ex vivo - it was a very nice study to express seven proteins at the same time, reprogram cells, and direct their differentiation - but all the cells were in a dish so maybe we would never have succeeded in getting it in in vivo. But there was enough work done prior to getting nucleic acids into animals and despite being such a gigantic macromolecule, it is possible. You only have to get through the cell membrane, you do not have to pass through the nuclear membrane since the ribosome lives in the cytoplasm. So, yes, it was pretty exciting.

How did you learn to navigate all of the steps from protecting the technology, to licensing it, and discussing with investors?

On the fly. Of course, we are not trained in how to do that at all, but ultimately the good news was that the science really spoke for itself, which really helps. Also, I was good at giving a science talk. I was at the Immune Disease Institute - now called the Program in Cellular and Molecular Medicine - at Boston Children's Hospital, and I presented this study at a monthly faculty meeting. Somebody made the suggestion to go tell Tim Springer - who is a great scientist and had great success in launching a company himself - about these studies and get his thoughts on this. I remember that it was a really odd meeting because he was being really aggressive with his questioning, about intellectual property, where is it going, etc. At the end of going through this strange meeting, Tim's visage totally changed with a big smile and he said that he wanted to invest in this. Tim became the first investor in Moderna, but he also helped me because he had done this before. He put me in touch with some venture capitalists and with Robert Langer, who is a prolific inventor at MIT and who agreed to co-found this company with me. It really helped to have a very experienced biotech entrepreneurs help me navigate the rest of the process. So, it was

fortuitous, connections, colleagues, the people around that have experience, and those mentors. It is really critical and to do it your first time would be very challenging if you were not doing it with somebody that has expertise and connections.

Do you think that academic researchers should be more active in translating their own research results?

Some discoveries are translatable, and they have a path to development for clinical application, but many do not. I spend a lot of my time looking at some really great science, and often the science is fantastic but difficult to move forward from the perspective of raising money and developing a clinical trial. However, sometimes discoveries come very much out of left field. CRISPR is a good example - bacterial immune system against bacteriophages. When it made the jump to human cells for targeted gene editing, it was very clear that now you can do something with that and indeed my lab was very involved in the early days. As soon as CRISPR jumped into mammalian cells, we were, I think, the first lab that took it in hematopoietic stem cells - we published a paper in Cell Stem Cell targeting CCR5 – work of Pankaj Mandal and others in the lab.

I think you need a little bit of a sense of - and this is hard - whether or not a really cool discovery has legs for translation. Most of the time, it does not, but sometimes it does, so you should certainly flesh out the idea and you should also talk to people who have that expertise on what it takes. As an academic scientist, you do not know what is needed to take one of your discoveries down the therapeutic pathway - you are just not trained in that. So, talking with people that are sure helps and generally speaking, everybody in the biotech industry have been in your shoes at one point, so usually people are pretty generous with their time and they will sit with you with your data. I do it literally all the time. For example, I have advised some people to do animal models and show me that the discovery that they make has therapeutic endpoints. They might take five years doing that and if that is the case, you do not want to start a company at that early point because that is five years of investor money and time that you are probably not going to get back.

There is also IP protection, but I think it is interesting to know that the CRISPR IP wars have not stopped multiple different companies going public and going into clinical trials. I find really interesting that the fundamental IP – for which there is a battle between UC Berkeley and the Broad Institute - is as yet undecided and that has not stopped these companies. I think that it says something about the importance of fundamental IP.

In the first few years of a start-up company, what do you think are the main challenges?

Fund raising and runway - you want to be very careful about not having only one month left and then all your money is gone. The team is so important - you want to work with people that have seen the movie before to know what is coming next. I think one important fundamental is: when you are first trying a platform technology that can be applied to many different things, you want to set the technical hurdles as low as possible for your first application. The highest bar might have the greatest clinical utility, but your chances of succeeding when you try to jump 10 feet over the bar are a lot less than if you are trying to jump over a 6-inch bar. As soon as you jump over the six-inch bar all, that money comes in because you have shown that you can do it, and now you can set the 1-foot bar, then the 10-foot bar. Really be careful about what you are setting out as your first clinical target and application, so that they are not unnecessarily technically challenging.

There are multiple companies that help you design a clinical trial depending on the size of your company, whether or not you have the in-house expertise and experience to do it, but you want to design it properly. It sure helps to get real experienced clinical experts looking at your design to say: “yes that is reasonable, but have you thought about this? This might be a better primary or secondary endpoint” and power it correctly. You brought it as far as getting patients and you have paid the money to run a clinical trial – the design must be good.

What set of skills would you encourage new investigators in hematology and stem cell biology to actively pursue?

Read outside of your field - be inspired by other ideas that you might be able to translate into your own work. Another one that I used to tell my trainees was: “We might have a really great idea and if you could succeed, it would be fundamentally game changing” but if you do not have a technological way to address that question, you have two options: 1) You can work on the technology to be able to get past that hurdle or 2) you can put that project on the shelf and wait until somebody else comes with the way to answer that question, then take it off the shelf quickly and answer the question. You have to know that there is a technically sound way to address the question. As scientists, we run into walls all the time, and there are two things to do: you can turn away or, if you have the persistence, the talent, and the creativity, you can actually chew your way through that wall – that may take a long time, so you need runway and you might need to be really creative to get your way through. I would think about this often when I was running in my lab as a young new investigator, and I would encourage others too.

Interview conducted by Dr François Mercier of the ISEH New Investigators Committee.

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