INTERVIEW

An Interview with Neurogeneticist Rudolph Tanzi

by Barbara Lom

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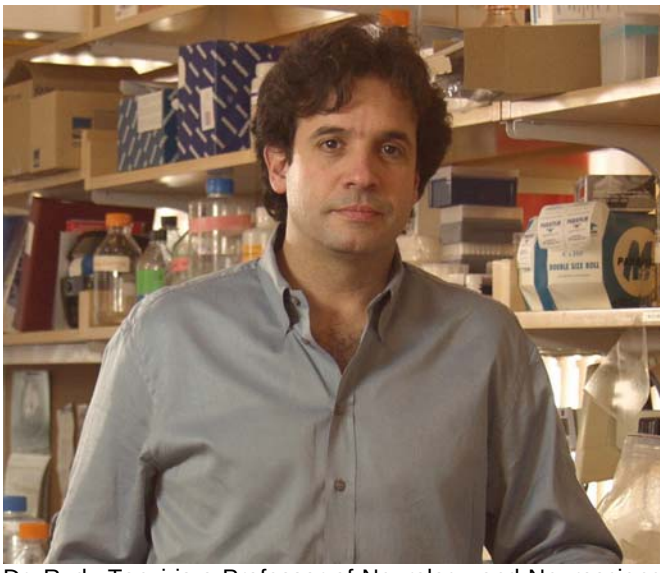

Dr. Rudy Tanzi is a Professor of Neurology and Neuroscience at Harvard University as well as the Director of the Genetics and Aging Research Unit at Massachusetts General Hospital. He has been a leader in the genetics of nervous system disorders since his first job in the lab of Dr. James Gusella as part of the team that identified the genetic basis of Huntington's disease. Since then his own lab has isolated multiple genes associated with Alzheimer's and other diseases. He founded two biotechnology companies that focus on developing treatments for neurodegenerative disorders. Moreover, Dr. Tanzi is a composer, musician, and author, recording his original piano music via *The Quiet Mind Project* and describing the process and excitement of human genetics research in a book, *Decoding Darkness: The Search for the Genetic Causes of Alzheimer's Disease*.

I had the pleasure of interviewing Dr. Tanzi in April 2005 during his visit to Davidson College to deliver the 2005 Smith Lecture. Dr. Tanzi impressed the Davidson community with his passion for understanding the genetic basis of human neurological diseases, his ability to communicate his research with a broad audience, his encouragement of young scientists, and his concern for patients and families. Moreover, he impressed me with his open and generous conversation describing his development as a scientist, his role as a scientific mentor in the lab, and his outreach to the public.

BL: Tell me about your family and formative years that led you to becoming a geneticist and neuroscientist.

RT: Like a lot of kids, I thought I was going to become a clinician. I came from an Italian-American family where, generations ago in Italy, my family was in academics. I have old relatives in Italy who actually made names for themselves in neuroscience. Eugenio Tanzi is considered by many the father of long term potentiation. In recent generations that came to the US, my father's father died early in life and my father was forced to quit high school. My mother worked in nursing first, and then medical transcription, so through my mom I had access to the medical world. They later started the first medical transcription outsourcing service in the country. The idea was that I would become a doctor, but then when I got to the University of Rochester in New York there was a whole concentration of professors there who were really some of the pioneers in early recombinant DNA and genetic engineering. I suddenly became immersed in what was a new field of recombinant DNA technology using genetic engineering. So I rapidly lost my interest in going to medical school and decided that I wanted to go into research and get into a field while it was very young.

BL: Is there anything in particular that you can point to that affected your trajectory?

RT: I was an undergraduate working in a laboratory. I was doing a simple project; we were just mapping genes in bacteria and I just really loved the simplicity and black-and-white nature of finding genes and then mapping them on their chromosome. I am a Virgo and I love order. At that time it was immediately gratifying and comforting to find genes and map them on chromosomes. I really got into gene mapping. I was in a program that, even though it was a bachelor's program, we took several graduate level courses at the medical school. I had a *Who's Who* of teachers. I got totally into the whole genetic engineering, recombinant DNA, and genetic linkage work, but at the microbial level. When I graduated from Rochester I decided that I was going to go to grad school, but that I wanted to take some time off, mainly because I was playing in a band. I was leading a band that was making good money and playing five nights a week in big clubs all through New England. I thought, I'm going to play music for a while because it's always been a love of mine and I'm not going to be able to do it later on in my life. I'll get it out of my system, but I'll work in a lab at the same time. I saw that Jim Gusella, who then had just finished his PhD, was looking to do genetics in humans. In the ad it said you needed to know how to use restriction enzymes, Southern blotting, working with human DNA, making DNA, *etc*. Even though these were not common things back then, I had learned them at Rochester in various labs I'd worked in. It turned out that Jim was looking for a post doc and I didn't even know the difference. I just said, "Look, I know how to do all this stuff. I can set up your lab." He was going to skip a postdoc and go right on to setting up a lab in genetics at Mass General. So I went there and, basically on a shoestring budget, set up this lab, literally bringing in

things from home. I brought in my Polaroid camera that my father gave me for my 11th birthday and took the red acetate that we used for the light show in the band and taped it to the lens to take pictures of DNA. Everything was makeshift – hamster cages to transfer DNA – whatever we could find. I realized that what Jim was trying to do was really special. It would be the first time ever that we were going to find variance in the human genome (at that time called RFLPs) and look for disease genes based on only having the blood of the family members and their pedigree. It's routine now, but back then, no one had done it yet. There was some progress on sex-linked chromosomes, but no one had gone into autosomes to find a disease gene. We were very successful, very fast. We were remarkably lucky that in the handful of variants we pulled out of the genome we found, not just one, but two were linked to Huntington's. One was only 150,000 bases away, that was G8. The next one, G9, was only 20 million bases away. Once we got the bigger pedigrees from Venezuela, if we didn't hit it with G8, we would have hit it with G9. So it was truly miraculous luck. At that time I wanted to carve out my own territory as a student and I moved to chromosome 21 and Down's Syndrome which eventually led the way to Alzheimer's.

BL: You were both a microbiology and history major. How did your history major contribute to your development as a scientist?

RT: I was concentrating on the history of science. I was very much into Thomas Kuhn and the whole idea of paradigms and paradigm shifts. The history work made me realize that most of what we believe in science is wrong. It gave me a perspective that said, 'Don't get too attached to what you learn as a scientist because a hundred years from now you're going to look really stupid.' It made me realize that small little things persist and continue. Small little findings that may mean nothing now will persist and drive the big findings later on. Most of the things we believe, our paradigms and belief systems, 120 years from now will be "cute." So it gave me that perspective to never get too hung up on one idea. As Jim Gusella said, "Never marry your hypothesis, only date it." Studying the history of science reinforced that the scientific method is only to prove the null hypothesis, which means that our goals as scientists are only to exclude our hypotheses. Our job is not to prove anything. When scientists, students, or postdocs come into my group there's often a trend. The MDs say they're going to prove this or going to prove that. I say it's just like when you have a patient, a diagnosis is based on exclusion. It's the same thing here. We have a question and you address a hypothesis by trying to exclude it. Whatever falls out, you take that tiny string and you run with it; but never get too close to your hypothesis such that you're trying to prove it or you're wasting your time.

BL: What do you enjoy most about your job?

RT: I love when I'm the only person in the world who knows something. I love it when there's a new discovery that you know is going to be big and is going to be a good paper and you're in your office and you're looking at the data and now you realize something. And you're all alone there with your cup of coffee. I know this and it is really cool and I'm the only one in the world who knows it. Of course, that only lasts for five minutes. The deeper part is just discovery and learning new things, discovering new things, and this infinite world of possibilities in nature to grasp onto anything where you can have a fairly good certainty that it is going to stand the test of time. One of the reasons why I do genetics is that hypotheses, paradigms, and theories are always going to shift, but no one's going to change the fact that one of the genes I found causes disease. I often think about science in terms of the order of questions. The order of questions in any field is usually: *where* and *when*, then *what*, and then *how*. As scientists we think we're talking about *why*, but usually we're talking about *how*. *Why* is usually for religion and philosophy. *How* is highly mutable. Whenever you've figured out how something works later on it's going to be modified. If you go after *what*s they're less mutable. I found this mutation in this gene APP or presenilin. It causes disease, that's not going to change. I enjoy being in a field where I can contribute to things that are not going to go away 120 years from now.

BL: You've trained a lot of scientists. You have a big group at Mass General. If you could change one thing about how scientists are trained these days, what would it be?

RT: Take chances. I think there's such a desire for security that many scientists get caught in prisons of linearity, whether it's how they develop their career or it's how they do their science. They want too much cause and effect, and get to the paper, and publish the paper, and build the CV, and do the post doc, and get the job. It's for security. My advice would be, remember to allow yourself to get lucky every day. You don't just get lucky; you have to allow yourself to get lucky. You have to remember to leave some breaks. To succeed you have to have some focus, there's no doubt you have to publish. The key is, as you're going along, allow yourself to free associate. You don't have to tell anybody about it. You can be an idiot all by yourself. Just sit in the corner and enjoy being an idiot and just free associate, but don't tell anybody. And then, later on, you're going to be looking at a result and because you had a synapse one day that had a particular free association you get an idea. I think a lot of serendipity favors the rehearsed mind. And the second piece of advice that I tell people is: do not try to control your experiments. Do not intervene with what you're doing. Just like the best musicians let the music take them, the best scientists let the science take them. Don't try to control the science, let the science take you. It's hands off. Science and nature are too big. Just enjoy the ride and see where it's going to take you. But that's all still part of taking chances. In our desire to have security and to fight fear of failure and our need for external validation and approval,

we often take very conservative and linear courses that don't leave room for serendipity and miracles. So you've got to leave yourself open to the miracles and to the magic.

BL: You've made a strong commitment to outreach. You've written a book for a general audience and you've been involved in *The Forgetting* on PBS. You have a lot of contact with families, patients, and the public. What's the one thing about Alzheimer's disease that you wish the public understood better?

RT: Clearly to not be ashamed of it. Unfortunately, you can't tell them, 'Make sure you go to the doc when you suspect AD, because we have drugs to cure you.' We have drugs that provide temporary benefit that are in the class of 'better than nothing.' There are trials that are going to occur. People in the public need to know that if they suspect a family member may have Alzheimer's that they should do everything they can to not be embarrassed by the fact that someone in the family has Alzheimer's. It used to be the same for cancer. When I was growing up they used to call cancer the 'C-word.' People didn't want to admit there was cancer in the family. We've gotten over that, but now it's an embarrassment to have Alzheimer's, the A-word. Alzheimer's is nothing to be ashamed of. It's a disease. It really is a physical thing. Alzheimer, when he described the first patient August D. in 1906, was suggesting that a mental disorder was due to physical lesions in the brain. He wasn't believed. People need to realize that there are physical things happening in the brain to cause the disease that cannot be helped. You need to get to a neurologist. Don't hide it. Don't mask it. A spouse should not try to mask it for another spouse just because they don't want the spouse to feel bad or don't want to admit it. Better to bring it to light and get some kind of treatment; and at least have your name in there, so when new treatments come up you have a chance to get them.

Secondly, that help is on the way largely from the genetic discoveries giving us points of certainty to work with and true targets, regardless of hypothesis that these are true targets and things are happening. I have two companies (one in Australia and one in La Jolla) developing two very different types of Alzheimer drugs, both of which are looking very promising. I think it's still a few years off - it's still probably at least five years off. People are sick of hearing five to ten years, of course, which is true, but it's getting there. My hope is that for my own generation and for most of the younger baby boomers we're not going to have to deal with this disease.