Andrea Ventura: Decrypting noncoding RNAs

Melina Casadio

Ventura explores the biological functions of noncoding RNAs in cancer and development.

Andrea Ventura grew up in Furci Siculo, a small seaside village on the eastern coast of Sicily, Italy. While in medical school, first in Sicily and then in Rome, he obtained a scholarship to study the biology of colon cancer with Dr. Richard Boland at the University of California, San Diego. This experience cemented both his passion for basic research and his desire to work in the US. After his MD and PhD, Andrea joined Tyler Jacks' laboratory at the Massachusetts Institute of Technology—his top choice for a postdoc, marking his return to the US. Since then, he's moved cities but remains passionate about living in the US and working on cancer biology. He now focuses on noncoding RNAs and how they shape cancers and development. We contacted him to learn more about his current interests and career.

When did your interest in science begin? What was your first experience of science?

I have been excited about science for as long as I can remember, but I believe three major factors fueled my passion. First, my father was a cardiologist and the village doctor, so I was always surrounded by textbooks of medicine and biology. Second, when I was 7 or 8 years old, my maternal grandfather (Vittorio) bought me a telescope and a subscription to a weekly astronomy magazine. I spent countless hours looking at the planets and my interest in science grew even further. Finally, I watched the TV show *Nel cosmo alla ricerca della vita* by Piero Angela, a sort of Italian Carl Sagan; I was absolutely fascinated by it. As soon as I learned about DNA and genetics, I was hooked and knew this was what I wanted to do in my life!

Where and with whom have you studied?

After medical school, I was accepted in the PhD program at the European Institute of Oncology in Milan, Italy, where I worked on the adaptor protein Shc, which had been shown to be involved in relaying signals from receptor tyrosine kinase receptors to Ras. Although my work didn't produce groundbreaking results, I learned how important it is to carefully choose the biological question one wants to address before delving into the experimental details. At the end of this experience, I knew I wanted to do a postdoc in the US, and I carefully planned a series of interviews on the East Coast, primarily in Boston.

At the top of my list was Tyler Jacks' laboratory at the Massachusetts Institute of Technology (MIT). Although I had contacted Tyler before, I never managed to get invited to visit his laboratory, I guess because my CV was not too impressive! But on my last day in Boston, I decided to show up at his office unannounced and somehow convinced him to give me a formal interview. I think he liked my perseverance and in the end gave me the job of my dreams: a postdoc position at the MIT Center for Cancer Research (now Koch Institute). In retrospect, this was by far the luckiest and most important event in my scientific career.

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What interested you about noncoding RNAs?

RNAi was discovered when I was doing my graduate studies, and I found it fascinating not only because of the opportunities it offered as a technology but also because it uncovered the fascinating world of short noncoding RNAs. As soon as I had the opportunity half way through my postdoc, I started working on it.

What is your laboratory currently focusing on, and what questions are you tackling next?

We have two main areas of investigation in the laboratory. The first is to keep exploring the biological functions of noncoding RNAs in cancer and development. This is something we have been doing from the beginning, initially focusing on oncogenic and tumor suppressive miRNAs, and more recently expanding on long noncoding RNAs.

Andrea Ventura. IMAGE COURTESY OF ANDREA VENTURA.

Our other research interest is about taking advantage of gene editing methods to create more accurate mouse models of human cancers, which we then use to better understand tumor initiation and progression and to test novel therapeutic strategies. As for what is next, I always find it very difficult to answer this question because the direction of my research tends to be swayed by serendipitous and unpredictable events. I find that in science, as in life, one can only plan so much. The only guiding principle I have is that I want to always be working on something that I am excited about. Life is too short to do boring things!

What kind of approach do you bring to your work?

I try to give my postdocs and students substantial freedom in coming up with new ideas and developing their projects. As long they want to work on something that I find exciting and that is somehow linked to our general research theme, I let them do it. I feel that my most important job is to help train the next generation of scientists. Of course, every student and postdoc is different, and some may need, at least initially, more direction than others. Figuring this out is not always easy, but I strongly believe that making mistakes is an essential part of becoming a good scientist.

I also try to keep a pleasant and cooperative environment in the laboratory. I am a strong proponent of collaboration and open science, and I have strong feelings about laboratories and institutions where people compete with each other and are afraid to discuss their ideas freely. The only two

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The Ventura laboratory. PHOTO COURTESY OF THE VENTURA LABORATORY.

things I require from my collaborators are scientific integrity and a true passion for figuring things out.

What did you learn during your PhD and postdoc that helped prepare you for being a group leader? What were you unprepared for?

Once I completed my medical training, I was ready to start my PhD but had very little bench experience. So, I learned how to run experiments. Perhaps the most important thing I learned was that, in science, choosing the right questions is more important and often more difficult than finding the answers! I spent many years working on a project I was not very excited about, and although in the end I learned quite a bit of cell biology, I decided that my next project would have to be something ambitious and risky that I found fascinating.

My postdoctoral training was by far the most important and exciting time of my scientific career. Tyler Jacks was simply an outstanding mentor. I like to think that I have learned a lot from him, not only about science, but also about how to run a laboratory, how to treat your colleagues, and how important it is to care for the integrity of the scientific process.

I found that starting my laboratory was much easier than I thought, and I got lucky because we were able to secure external funding rather quickly and published our first paper within the first year. The first three people who joined my laboratory, a technician who is still with us (Paul Ogrodowsky), a student who is now on the job market for an independent position (Ping Mu), and a postdoc who is now a successful scientist at Pfizer (Yoon-Chi Han), were incredibly talented and hardworking. I owe whatever success I have had as a principal investigator (PI) to their willingness to take a chance and join the laboratory of a young and unknown PI.

What has been the biggest accomplishment in your career so far?

I would say that our work on the miR-17∼92 cluster and on in vivo somatic genome editing has placed my laboratory on the map. The work on miR-17∼92 in particular took an amazing amount of effort by several postdocs and students; we generated and extensively characterized six knockin mouse strains, which in the pre-CRISPR era was quite a feat! The study of these models has already provided useful insights into how a miRNA cluster controls gene expression in vivo and I suspect we will continue learning from them (1, 2).

Our recent work on somatic genome editing is also very exciting. We were the first to show that in vivo delivery of CRISPR/Cas9 can be used to engineer chromosomal rearrangements in otherwise wild-type mice, and we have used this strategy to generate models of lung and brain cancer (3).

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What has been the biggest challenge in your career so far?

The need to constantly be writing grants to make sure I have enough funds to run the laboratory is certainly the greatest challenge I have faced. It takes away some of the fun of doing science and adds unnecessary uncertainty to what otherwise is the best job in the world. That said, I am convinced that scientists are very privileged people, as we basically get paid to have fun!

What is the best advice you have been given?

"Don't think about tenure, just do good science and have fun."

What hobbies do you have?

My hobbies have evolved quite a bit overtime and range from playing volleyball and soccer (when I was younger), billiards, and (trying to play) golf. I have been playing chess for many years, and I really like the fact that it is one of those games where luck plays absolutely no role. More recently, I have become involved in the world of simulated (sim) racing, where people compete online driving virtual racecars. It is my nerdy side, but I find it very relaxing and I enjoy the engineering and competitive aspects of it.

What do you think you would be if you were not a scientist?

Professional soccer player (just kidding!). More seriously, I think I would have put my MD to good use following in my father's footsteps. I am also fascinated by computers and I enjoy writing work-related scripts in Python and R or simple programs in Swift and Objective C. Perhaps I would have enjoyed a programming job.

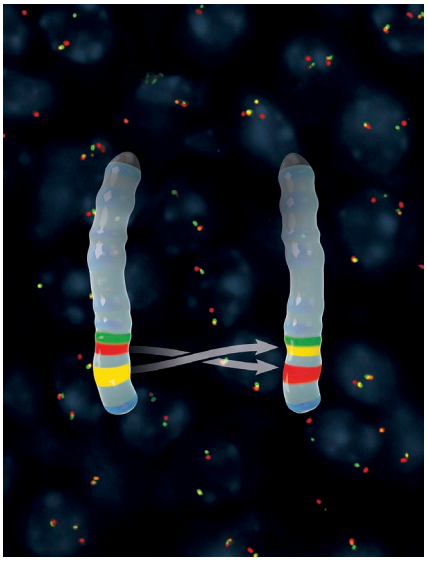
What has been your biggest accomplishment outside of the laboratory?

I was a runner up in the Lotus 79 iRacing championship in 2014!

Any tips for a successful research career?

I'll give tips to others when, and if, I am ever successful!

1. Ventura, A. et al. 2008. *Cell.* 132:875–886.
2. Han, Y.C. et al. 2015. *Nat. Genet.* 47:766–775.
3. Maddalo, D. et al. 2014. *Nature.* 516:423–427.



Schematic of a chromosome undergoing a CRISPR-mediated inversion. The background is a three-color interphase FISH detecting the Eml4-Alk inversion performed in the Ventura laboratory. IMAGE COURTESY OF ANDREA VENTURA/MEMORIAL SLOAN-KETTERING CANCER CENTER.