Dankesrede
von Prof. Andrew Z. Fire

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Es gilt das gesprochene Wort!

I love my job.
Consider that you might get up in the morning with the luxury to think about how the world works. Not the whole world, as this would be too much to contemplate before breakfast, but just a little piece that you can put under a microscope. How can I watch this piece of the world a little more carefully? What can I do to just slightly nudge it, then see what happens? How does this piece of the world affect the mini-microcosm around it? What would happen if this tiny part of this piece of the world were not there?

My piece of the world is innocuous.
The smallest of small, tiniest of tiny creatures. A worm that you can't see, and probably would never need to. Living in the soil, the worm's cousins frolic in the subterranean company of other dirt-dwellers. Their main goal in life is to find tasty offerings among the (even smaller) life forms in the dirt and to then reproduce with abandon. Three generations of scientists, starting with the imposing figure of Sydney Brenner in Cambridge, have used this worm to seek a piece of the world that they guessed they might understand. Over forty years each of us chose this particular beast for a different and very personal set of reasons. Nonetheless each of us benefits in our day-to-day inquiries from the fruits of each others labors.

How does this sound to you, an audience engaged laudably engaged in the day-to-day exercise of human commerce? How does this sound to my two children, four and six years old, who are just accustoming themselves to the macroscopic world and to their place in it? What language could I have used to explain it to my grandfather, who for a time manufactured hats in the Black Forest, just a few miles from here?

Science starts with questions.
On a day to day basis, what challenges us as scientists is not a lack of answers but a lack of the appropriate questions. But I presume considerably to call myself a scientist. Science is not defined merely by turning over a series of stones to see what lies underneath but rather by choosing which stones to turn over and by the process (at least) of trying to draw a larger picture from what we observe. Coming from training in mathematics and biochemistry, the concept that one could begin to understand a whole animal was exciting and enticing. Could we really understand each and every aspect of the animal's life and death? What stones did we need to turn over to acquire real and meaningful understanding? What understanding could be meaningful if we're talking about objects that are too small to be visible?

Science is not cheap.
For twenty years, I have managed a research laboratory with the generous support of the United States Government, in particular the National Institutes of Health. Investigating biology is a satisfying pastime to me, it is still quite fair to ask why a government which has many other obligations and objectives should support this. The answer to this is that *we, as humans, are biology*. Our birth, life, and death, our fortitude and sickness, even our response to the world are all biology. We can choose not to understand how our own bodies and minds work, but this would not be human nature. It would also deprive us of two essential qualities of life: trying to understand ourselves and making every effort that

we can to intervene when disease threatens to take from us what we value most. We are not worms, but many of the processes that go on in our cells are similar to equivalent processes in worms, flies, mice, fungi, and even bacteria. The track record of research with the various tiny "model" organisms has been great. We owe important pieces of what we know about human biology in large part to what has been learned from worms and their brethren. This certainly doesn't mean we understand everything; it also doesn't mean that all biology can be understood by turning a few worm-stones over. Nonetheless, all of us who do biology can take considerable satisfaction in the degree to which a relatively small community has contributed both to fundamental understanding and to increasingly effective medical intervention.

Scientific discoveries originate from a community.
I still have not fully explained why I enjoy my job... Going each morning into a darkened room with no other people to talk with would be both boring and depressing. Instead, I have the good fortune to spend much of my day listening to, speaking with, and corresponding with a wide variety of colleagues over questions of scientific fact, experimental design, and analysis of what lies under the rocks that we have turned over. In my case, the colleagues are peers at a wide variety of career stages who can be called students, faculty, postdoctoral fellows, or occasionally just staff. As noted above, much of what we contribute to each other are questions. At the most advanced level, a postdoctoral fellow might be expected to ask for guidance on the details of designing or interpreting a series of experiments, a graduate student might be expected ask what approach would be most informative to open the door on a series of interesting questions, an undergraduate might be expected to ask what those questions might be, and a secondary student might be expected to ask why we care. In the best of all possible worlds, every individual scientist at every level should expect from themselves and each other continued inquiry at each of these different levels. Certainly as faculty, this is our goal in our own work and in our teaching. I have been fortunate in my career as a scientist to be surrounded by teachers, colleagues, and students at all levels who have kept this spirit of inquiry and who didn't feel constrained by their status to play only one specific role.

Science is not a linear process.
Did I say that science can also be difficult? Nature does not give up her secrets easily. We labor for a long time, sometimes days, sometimes weeks, and sometimes decades with one view of how the world should work. Often our view is partially correct, always it is incomplete. What if the experimental results don't come out the way we expect? Was our original incorrect? Was our expectation of experimental simplicity naive? Was our experimental technique flawed? Or perhaps is there some really fundamental lesson rising from the ashes of our misunderstanding? Should we ask only questions that we can answer or only questions that we cannot? When will things make sense? At the same time as these challenges are frustrating, they are also an opportunity.
As long as we get unexpected experimental results, there is still something to learn. Pat a different way, sometimes when you need to find something in the dark you look a little harder. Although our contributions, such as they have been, to the chemistry of the RNAi trigger stood on the back of two decades of training in biochemistry, molecular biology

and genetics, the choice to work on a novel and uncharacterized biological phenomenon came from a mixture of hope, impulsiveness, curiosity and responsibility.
In the mid 1990, an unexpected set of experimental results formed a communal dataset shared by a small but international group of scientific laboratories studying a set of processes that we now call 'RNAi'. Nothing really made sense, a situation that scared much of the 'respectable' scientific world away from research in the area. From my perspective, having worked on-and-off in the field (years before) without being able to make a significant contribution, it wasn't clear that this was an appropriate area for the use time and resources. What (if any) experiments could be done? What could *we* do?, and How could any model explain the puzzling and perplexing array of experimental data that had been accumulating? There were certainly a sufficient number of ongoing "safe" projects in the lab to ignore the odd results here. Despite the intriguing research appearing from Dr. Mello's group and from other colleagues, I suspect that I would have circumvented rather than wading into this complicated area of research.
But there was another inducement, coming from outside of science and outside of the lab. As biomedical scientists, we often justify our work in part as an endeavor aimed at understanding and conquering disease. The argument is easy to make if you are in the lab or are writing a research grant. And it's a valid argument. As I've said, much of what we know about disease comes from experiments carried out by biologists just wanting to know how things work in nature. But when it comes down to a real understanding, 'everything' we know about certain diseases is really not much. Metastatic cancer is such a disease and in early 1997 I was watching four close friends deal with its effects. I am sure that many of you in this room could insert in their place your own group of friends or family who have been so affected. I am certainly not a clinician, so when I would ask myself "Is there anything I can do?" the answer was always a disappointment. Working on a completely unexplainable biological phenomenon was at the time, for me, an expression of hope that somewhere in the biological world there would be answers to the difficult questions that occur as we confront this and other devastating diseases. I stress the non-linearity again of research. Although the discoveries made by the many laboratories working in this field may eventually make a contribution to treatment of cancer, three of the four friends who I watched dealing with the disease in early 1997 died that year while the fourth was cured by "standard" therapies. Although any connection here is a purely coincidental one, I cannot think back to the time of the discovery of the RNAi trigger without thinking of the lives of these four individuals.

Watching science develop is exciting
A new set of researchers had begun to study gene silencing by double stranded RNA before the ink had even dried on the first published reports of these effects. Science as a community endeavor requires as wide a variety of different outlooks as humankind can provide. For the RNAi field, this has meant chemists, pharmacologists, computer scientists, physicists, molecular biologists, plant breeders not to mention the dermatologists, cardiologists, pathologists, and the occasional ecologist. Much of my energy in the past decade has been taken up, of course, with continuing the research effort of my modestly sized and modestly resourced laboratory. At the same time it has been extremely exciting to watch as the field moves forward with a speed that no legitimate scientist would have predicted in 1997. Of course we are still in the dark about

many aspects of this field. Nevertheless, what we have learned has been a source of vicarious pride to me and I hope as well to the many other individuals who worked in this field for one year or twenty.

Novel capabilities arrive with novel responsibilities

Do we look at the last decade of work in this field in terms of understanding a new set of natural processes of the cell, or do we say that nature has given mankind a gift? Whatever the perspective, we now have a biological capability that was previously only hypothetical: we can remove specific RNA transcripts from living cells. What responsibilities for those of us in the RNAi field arrive with the new capability?
First, knowledge of this process is only of value if it is widely held and broadly based. We need to explain publicly not only the significance and impact of the new capabilities but also their limitations, uncertainties and potential dangers. At present, the situation is as follows: although we have seen that discoveries made with and about the RNAi machinery will play a major role in directing novel medical research, we can't say that any single disease will be cured by RNAi. But the hope is real. We thus need to find ways to convey the challenges along with excitement that has arisen.

Communicating the details of a few discoveries is not our only responsibility. As scientists, we need to explain the need for continued commitment to supporting research by meeting nature on her own terms. The vast majority of major biomedical advances have come from research that was directed at understanding nature, and not at validating any individual short term treatment candidate. We need to constantly stress the value of both basic and applied research so that neither is a casualty of public excitement over a few recent discoveries (from basic research) or promising results (from preclinical trials).

Science is not property, nor are ideas, but inventions are. Management of intellectual property is an essential component of technology development. Competition between different approaches and different groups of investigators can likewise be a very valuable stimulus to rapid development of the technology. At the same time, it is critical to recall that competition and intellectual property ownership are designed to facilitate and not inhibit communication and collaboration. Particularly as researchers with some history, and perhaps a bit of perspective in the field, we need to ensure that personal and company relationships among the individual players in this area are sufficiently close and trusting that technologies that need to be practiced and combined in various ways are available to anybody who could use them. This has worked remarkably well (under the circumstances) in the first decade of the RNAi field and I hope it will continue to.

Finally, as scientists in we have a responsibility to pass all of the mixed emotions involved in new discovery to our children and to the whole of the next generation. Thus the joy of exploration, the gratification of discovery, the need for critical thought, a respect for those who know more about a subject than we do and for those who know less, the responsibility to see discoveries used for positive benefit, and a hope for the future.

Thank you for the time.