EMBO reports

The A-T gene hunt

An interview with Yossi Shiloh on decision making, the discovery of the ATM gene and the lessons from genetics

Esther Schnapp & Holger Breithaupt

EMBO reports (ER): Your group discovered the ataxia–telangiectasia mutated (*ATM*) gene, via positional cloning. Can you tell us the story?

Yossi Shiloh (YS): The story begins in the summer of 1977, long before I had my own group. I had just completed my MSc in human genetics at the Hebrew University in Jerusalem. My mentor was the late professor Maimon M. Cohen, a renowned cytogeneticist, who accompanied me throughout the decision process about the subject for my PhD thesis. One evening, he asked me if I could join him on a field trip the following day. "It's going to be a two-hour drive to a small village in the southern part of Israel inhabited by Moroccan Jews and we suspect that several children in a family there might be affected with the genetic disorder, ataxia telangiectasia." I didn't know much about ataxia–telangiectasia (A-T), but quickly grabbed some reprints and could feel my eyes getting bigger as I read. A-T seemed to be a cruel, extremely complex disease, with a broad array of symptoms, all of which apparently boiled down to one gene with autosomal recessive inheritance. It leads to progressive, severely debilitating cerebellar degeneration causing the ataxia, which relentlessly develops into a severe neuromotor dysfunction; dilated blood vessels observed primarily in the eyes (telangiectasia); chronic lung disease; predisposition to lymphoreticular malignancies; thymic and gonadal atrophy; endocrine abnormalities; chromosomal instability; and acute sensitivity to ionizing radiation. We now also know that an important component of the disease is premature aging.

A girl from that family had just been diagnosed with lymphoma at a local hospital, but the doctors there noticed a more complex display of symptoms and suspected A-T. Since the family had 10 children, we expected additional patients. We met the parents at the family home and noticed a few unaffected children playing in the backyard. The parents were not welcoming. They were not ready to accept the notion of a genetic disorder in their family and insisted that the daughter in the hospital was the only one in the family with that disease. We finally gave up and were leaving, making our way out through a narrow hallway, when Maimon caught my hand, whispering "Look!" Through an open door to a dark room, I could barely see a boy and a girl sitting on a couch, with something strange about their faces. We turned on the light and I saw their bloodshot eyes: telangiectasia! When Maimon helped the boy take a few steps, I saw ataxia for the first time. A school bus stopped outside, and one of the healthy brothers helped another A-T patient climb the steps. Four of the 10 children were affected with the disease.

> *"A-T seemed to be a cruel, extremely complex disease, with a broad array of symptoms, all of which apparently boiled down to one gene with autosomal recessive inheritance."*

As we drove back we didn't speak much, but when Maimon dropped me at home I said, "I think I have the subject for my PhD thesis". The following morning I began to work on A-T, and have been at it ever since. Much later, I remembered that on our way to the village Maimon had said, "Choosing a subject for your PhD thesis, and your work later, are important decisions. Do you want to work on a 'big' important but difficult problem? If you do, you might fail and your work won't be remembered. But if you succeed, your contribution will be significant". That statement sounded obvious at the time and I didn't really grasp its subtext, but later on, when I reflected on that trip, I understood what he meant. By then, I had seen many more A-T patients in Israel: North African Jews, Palestinian Arabs, Druze, Bedouins. A-T has been found worldwide in many human populations, at a frequency of 1:40,000 – 1:100,000 live births, with marked occurrence in several countries including Israel.

> *"When Maimon helped the boy take a few steps, I saw ataxia for the first time."*

My PhD thesis was subsequently carried out under the supervision of the late Yechiel Becker, who was enthusiastic about investigating A-T and gave me a free hand to explore the cellular phenotype of the disease. The hallmark of that phenotype was the extreme radiation sensitivity of A-T cells, first reported by Malcolm Taylor in the UK. We and other laboratories understood that it reflected a profound defect in responding to double-strand breaks in the DNA. I noticed, however, that A-T cells were also moderately sensitive to other DNA damaging agents. But without information about the mutated gene and its protein product, not

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Dr. Yosef Shiloh is Myers Professor of Cancer Genetics and a Research Professor of the Israel Cancer Research Fund, at Tel Aviv University Medical School. He obtained his PhD in Human Genetics at The Hebrew University of Jerusalem. He trained further at Harvard Medical School, the University of Michigan, New York University Cancer Center and Memorial Sloan Kettering Cancer Center in New York, and was a Fogarty Fellow at the US National Institutes of Health. He is a member of The Israel National Academy of Sciences and Humanities and won the 2005 EMET Prize in Life Sciences (Israel), the 2011 American Association of Cancer Research G.H.A. Clowes Memorial Award for Outstanding Accomplishments in Cancer Research, the 2011 Israel Prize in Life Sciences and the 2015 Olav Thon Prize in Natural Sciences and Medicine (Oslo, Norway).

Yosef Shiloh has dedicated most of his scientific career to understanding the genome instability syndrome, ataxia–telangiectasia (A-T). He began his work on A-T while working on his PhD thesis, and this quest culminated in 1995 in the identification of the responsible gene, *ATM*, in his laboratory. The laboratory has since been studying the function and mode of action of the *ATM* gene product—the ATM protein while continuing its quest to understand A-T. In addition to his research, he devotes considerable time to giving popular scientific lectures to the general public and high school students on the medical, social, and ethical implications of the genome revolution. He is married to Prof. Shoshana Shiloh of Tel Aviv University's School of Psychological Sciences, and they have two children and two grandchildren.

Dr. Yossi Shiloh with Dr. Yael Ziv, the Shiloh laboratory manager. Photograph by Ayelet Klartag.

much more could be understood about the disease. The positional cloning approach was just emerging and was based first and foremost on classical genetics.

ER: How was it to do genetic research in the 1970s and 80s?

YS: During my PhD studies, we used the technology and the means that were available at that time. We raised cell lines from patients and controls, and most of our work focused on measuring their sensitivity to radiation and other DNA damaging agents. During my postdoc training at Harvard Medical School with the late Sam Latt, I practiced recombinant DNA technology, which was rapidly changing research in the life sciences. I investigated DNA amplification in cancer, but kept working on projects associated with A-T. In those years, the concept and technology of positional cloning continued to develop, leading to some of the famous "races" to identify major disease genes. One of the greatest discoveries in that area was in the making on the other side of my bench: Lou Kunkel and Tony Monaco were discovering the Duchenne Muscular Dystrophy (DMD) gene on chromosome X, based on the large deletions that constituted a major fraction of DMD mutations. Watching this breakthrough take shape right next to me was not only inspirational. Lou's and Tony's experimental approach later had a major impact on our work, coming at probably the most critical stage of our search for the A-T gene. Reflecting on my training as a scientist, I am extremely aware of my luck to have had wonderful mentors and training environments.

By that time, A-T had been found to be genetically heterogeneous. This meant that in each affected family, one gene was responsible for the disease, but different genes could cause the disease in different families. Other genome instability syndromes with such heterogeneity are xeroderma pigmentosum and Fanconi's anemia. When a disease is caused by interference with a cellular circuit operated by several proteins critical for its function, or by inactivation of a protein complex with several subunits, mutations in each of the corresponding genes can cause the disease. The data on the genetic heterogeneity of A-T were rock-solid, having been generated independently by two excellent laboratories in the United States and Europe. Their finding that there were four complementation

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groups in A-T, presumably representing four different genes responsible for the disease—*ATA*, *ATC*, *ATD*, and *ATE*—was readily accepted by the field. This had critical implications for their positional cloning: A-T families had to be "typed" according to their complementation group before they could participate in linkage studies. Linkage analysis was the starting point of a positional cloning effort, and families belonging to different complementation groups, presumably representing different mutated genes, could not be pooled together for this analysis. It was clear that mapping and identifying these genes would be a long and arduous journey.

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In 1985, I established my laboratory at Tel Aviv University, which has been my professional home to today. This was a joint effort of me and our dedicated laboratory manager since then, Dr. Yael Ziv. In order to have a dynamic beginning, we initiated several projects while we traversed the country collecting blood samples and establishing cell lines from the A-T families. We knew that the Moroccan-Jewish families belonged to Group C, thus representing the elusive *ATC* gene, and the Palestinian Arab families represented the *ATA* gene. A breakthrough in the field came in late 1988, when Richard Gatti of UCLA mapped an A-T gene, presumably *ATA*, to the long arm of chromosome 11 based on linkage analysis using a cohort of Group A families. That landmark discovery initiated a massive effort to identify the A-T genes. While reminiscent of the positional cloning races underway in laboratories worldwide, the effort of A-T investigators had some unique characteristics: The American, European, and Australian groups involved in the effort were meeting regularly in A-T workshops and sharing information and reagents. This went on in a cordial atmosphere for the 7 years from the initial mapping milestone to the identification of the *ATM* gene. In retrospect, I know how remarkable and important this aspect of our "race" was.

At that time, we closed down all our "bread and butter" projects, and the entire group plunged into this single effort. It could be argued that the decision was somewhat irresponsible, but my commitment to understanding A-T had long been solid and I knew it was a long-term one. My enthusiastic and dedicated group readily embarked on this risky path.

We first went back to the DNA samples from the Moroccan-Jewish family that I had met back in 1977—a family that had been typed to "Group C", like the other Moroccan-Jewish A-T families. Using the chromosome 11 genetic markers, we obtained a striking finding: The responsible gene in that family—presumably the *ATC* gene—fell into the same region on chromosome 11 to which the *ATA* gene had been mapped. Similar studies by other groups suggested that, in fact, all four A-T genes were located in this same region. However, given the solid complementation data, we still had to assume that there were four different A-T genes, perhaps closely linked on the long arm of chromosome 11. We now had to narrow down that region. So, we cloned a 10-megabase portion of chromosome 11 in overlapping yeast artificial chromosomes, generated new microsatellite markers within that region, and repeatedly used them in linkage analysis of our growing cohort of A-T families in order obtain a smaller candidate region, which we finally cloned again in overlapping cosmid clones. These days, when I tell the story to graduate students, they shake their heads: They know they can get full sequence and gene content of any portion of the human genome with a few keyboard strokes.

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In 1991, it was time to learn how to fish out genes from that long genomic region. I took a sabbatical year in the laboratory of Francis Collins, now the NIH Director, in Ann Arbor, where Francis developed a "gene hunting" technique that constituted a quantum leap in the positional cloning approach. For a year I was at the bench again, and once again was enveloped in an extremely inspirational and congenial atmosphere. I came back to my laboratory with a valuable asset: a series of genomic fragments that represented transcribed sequences within the critical region to which we had mapped the A-T gene cluster. These fragments later served as baits for fishing out the corresponding cDNA clones.

I would like to describe an interesting moment around the fourth year of our effort, which I remember vividly. I gave a seminar at one of our universities, describing the long journey of positional cloning, not concealing the difficulties and uncertainties. One of the professors in the audience got up and asked the first two questions. The first one was, "Why do you work on a rare disease that only few people know about?" I said, "I have two answers for you: The first is that, yes, this is a rare disorder but it's a terrible disease and an enormous hardship for the patients and their families. They really don't care if it's rare or common. Patients and families with such 'orphan diseases' deserve our attention, work and resources same as patients with more common diseases. My second answer to this question is related to that day in the summer of 1977, when I first saw that stunning combination of symptoms affecting so many body systems. Clearly, if we find the underlying cause of this disease and identify the responsible gene, we will have identified a very important biological function with far-reaching implications, not only for A-T, but also for many areas of medicine. So even if there was one single patient with A-T in the world flagging to us that elusive gene, that should have been sufficient for us to want to get that gene". The second question was, "Given the challenge of positional cloning and the competition, what makes you think that you will be able to do it?" I responded: "There's absolutely no guarantee that our group will be the first to identify any of the A-T genes, and other groups might be the winners. But I've been in A-T research for more than 16 years now, and always wanted to do what was most important for advancing A-T research. Clearly now is the time to identify these genes. We have the concept, the tools, and a wonderful team to do it, so this is what we're doing".

ER: How was it when your group finally identified the A-T gene?

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YS: When I give a lecture to lay audiences, I build it as a story about decisions. How do scientists decide what to investigate? How do they make decisions at important turning points? And the turning point in our work was obviously the moment of the gene discovery. In late 1994, we had a red herring: It was a DNA helicase gene within the critical A-T region, which had an in-frame three amino acid insertion in some A-T patients. A DNA helicase made a lot of sense, but an in-frame insertion was not a convincing disease-causing mutation. We had a large collection of unrelated DNA samples and quickly tested them for the presence of this insertion. It turned out to be a rare polymorphism unrelated to A-T. At the same time, a graduate student in the laboratory, Kinneret Savitski, had just identified a big cDNA clone, close to 6 kb, which was encoded by another gene in the A-T region. Northern blots revealed a corresponding huge mRNA, about 13 kb in length. As we were slowly sequencing it (using sequencing gels), we noticed a PI3-kinase domain: a large signaling protein! At this point, my postdoc training became important: I remembered how the DMD gene had been identified based on its deletions in the patients. DMD was an exception with regard to the number of deletions that caused the disease, but such deletions were occasionally found in other genetic diseases, and could be readily identified using Southern blots without initial sequencing. So we routinely hybridized our candidate cDNAs to Southern blots representing A-T families. We called them "family blots". One day in early 1995, Yael and I were looking at one of her family blots which she had just probed with the PI3-kinase cDNA clone. It represented a large Palestinian Arab A-T kinship of Complementation Group A, and we knew that the patients in that family should be homozygous by descent for their A-T mutation. Several bands were strikingly missing in every one of the patients, and we could even see that these bands showed lower intensity in patients' parents compared to unrelated controls. It was a large deletion clearly segregating with the disease! For a moment, I lost my breath but tried to stay calm and just suggested that the experiment will be repeated with additional patients from that family and additional controls. But, Yael and I knew the result was unequivocal: We had just identified the *ATA* gene!

ER: How did that turn out?

YS: Here we're going back to the matter of decisions. This startling finding was associated with the toughest and probably most dramatic decision I had to make as a scientist. Clearly, the next thing to do was to push out a paper as quickly as possible. There was a sense of urgency in the air: We had just heard through the grapevine that one of the A-T genes had been identified by another group and their paper was under review.

> *"I knew that the immediate implication of identifying a single gene for A-T would be reliable prenatal diagnosis for this disease in all A-T families around the globe..."*

I was awake the entire night after finding the deletion. I thought, okay, we have the *ATA* gene. But what if, after all, there are not four A-T genes, and this is simply *the* A-T gene, the one and only that is responsible for the disease? The primary reason for this tormenting thought was not that if it was a single gene its publication would save the field from chasing three additional genes. It was my education as a human geneticist, and the many hours I had spent as a graduate student in the clinic listening to family stories. In those days, genetic counseling meant explaining the disease and its mode of inheritance to the family and providing the recurrence risk: for example, 25% risk in each pregnancy when the disease was autosomal recessive. When the responsible gene was not known and there was no reliable assay for prenatal diagnosis, the parents had to make a very painful decision about whether or not to have more children, taking the risk of having additional patients in the family. I knew that the immediate implication of identifying a *single* gene for A-T would be reliable prenatal diagnosis for this disease in all A-T families around the globe, without the need to wait until all four genes are identified. In fact, several microsatellite markers that we had located within and around the PI3 kinase gene could be readily used for prenatal diagnosis and carrier detection in A-T families if this was the only gene responsible for the disease. Once again I reflected on what Maimon had said to me about tackling tough problems: Indeed, defining the PI3 kinase gene as the only A-T gene would constitute a more significant contribution than publishing it as the one-of-four, the *ATA* gene... But this would obviously come with a cost: a high-risk gamble, more work with highly uncertain results—we would need to show mutations in this gene in patients assigned to all complementation groups while having only half of the mRNA sequence—and, of course, delaying our publication.

I thought that such a decision should be made collectively by the group. I brought the issue to a special group meeting, which turned out to be one of the most tense meetings we had ever had. I explained the considerations, the risk, and the potential benefit. The decision was made not to publish the "*ATA* gene", and instead try to identify mutations in this gene in patients representing the other three complementation groups and additional Group A families. The mutations appeared, one by one, in all patients of all groups. We had *the* one and only, single A-T gene! We called it "A-T, mutated—*ATM*". The information required for molecular prenatal diagnosis of A-T was included in the gene discovery manuscript. Prenatal diagnosis of A-T was initiated right away after its publication, in numerous medical centers around the world including Israel. The family with the deletion was among the first Israeli A-T families to benefit from the new service, which was readily provided by the local hospital.

> *"I should mention again that the quest for the A-T gene by several groups was conducted in a friendly atmosphere and relationships among the competitors remained cordial..."*

I should mention again that the quest for the A-T gene by several groups was conducted in a friendly atmosphere and relationships among the competitors remained cordial—not common in such situations in those days. It was essential to keep it that way. As we were writing the paper, I picked up the phone and called the other runners in the race: "We have a gene that is mutated in all four complementation groups of A-T".

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Their reactions were noble and expressed genuine satisfaction with the finding and recognition of our work. These telephone conversations corroborated my decision to make this, as much as possible, a happy end for everybody by having these colleagues—many of whom had by then become friends—co-author the paper. This decision was an easy one, and the field celebrated and began making preparations for the next stage: studying the ATM protein.

"… in my mind the happiest moment in science is not when your own idea turns out to be true, but when your student comes up with a brilliant idea that turns out to be true."

ER: What challenges did that present?

YS: While continuing our molecular genetics work on the *ATM* gene structure and A-T mutations, we, like many others in the field, were switching gears to protein chemistry. I had been trained as a human geneticist, and molecular genetics techniques had been the core of our laboratory since its inception. It was clear, however, that further understanding of A-T would come only by moving into signal transduction and studying the ATM protein. Soon after making this switch, we and other groups were met with another surprise: while ATM bores the P13 kinase motif, it turned out to be a protein kinase. A natural candidate ATM target was the p53 protein. Three years earlier, Michael Kastan's laboratory in the United States had shown that p53 was a pivotal player in a cell cycle checkpoint activated in mammalian cells in response to treatment with ionizing radiation—the DNA damaging agent to which A-T cells were so sensitive. That landmark paper showed that the level of p53 rose rapidly in IR-treated wild-type cells, but the entire pathway was blocked in A-T patients' cells. Our experiments indicated that p53 was indeed a physiological substrate of ATM. We were wondering whether the level of ATM too rose in irradiated cells, but it didn't—instead its *activity* was enhanced. ATM was thus activated in response to IR-induced damage. Naturally, the Kastan laboratory was following the same line of thinking, and when Michael and I compared notes, the datasets were similar and led to identical conclusions and two back-to-back papers. We were now a signal transduction laboratory, and the road was open to identifying additional ATM-dependent pathways and studying their functional significance. We are doing this till today.

It quickly became clear to us that ATM governs a complex network of pathways in response to DNA damage. To obtain an overview of this network, we had to teach ourselves systems biology and plunge into "omics" methods, such as proteomics and transcriptomics. This while continuing to study individual signaling pathways in the ATM-mediated DNA damage response. Many laboratories have now shown that ATM also has other roles in cellular metabolism, such as maintenance of redox balance, mitochondrial function, NAD^+ levels, glucose metabolism, and others. ATM turned out to be a homeostatic protein kinase.

But, we made this journey in order to understand A-T, and perhaps contribute to finding treatment modalities for the disease, which are still lacking. Many A-T symptoms can be explained by the myriad functions of the ATM protein, but the molecular basis of a major symptom—the relentless cerebellar atrophy—is still unknown. Hypotheses are being examined in various laboratories, including neuron-specific functions of ATM that are not associated with the DNA damage response, or its other metabolic functions. For us, the burning question of what accounts for the cerebellar atrophy posed another "big" difficult problem that required learning yet another experimental paradigm. Again, I remember Maimon Cohen's words to me about such problems, back in 1977. So, in order to test our own theory, we again acquired yet another whole set of experimental methods: generating and working with mouse models, and studying cerebellar biology with neuroscience tools. This major undertaking was possible with the generous help of dedicated collaborators such as Ari Barzilai of our university, a neuroscientist. Once again we are on the steep side of a learning curve.

ER: The story of the discovery of the A-T gene is a typical human genetics family story. What do you think is the value of family studies and classical genetics today in light of the state-of-the-art technologies: metagenomics, high-throughput, full-genome sequencing, GWAS?

YS: When I mention the positional cloning story in seminars I say, "We now have the results of the Human Genome Project, but the basic concepts and technology that enabled it were established in numerous individual laboratories searching for single-disease genes, each one doing its own genome project. At some point, positional cloning efforts became simpler, since the human genome sequence readily allowed testing candidate genes known to reside in a region to which a disease gene was mapped. These days whole-exome sequencing makes disease gene discovery much faster, often eliminating the need for genetic mapping. It's gratifying to see these developments despite seeing positional cloning becoming history". Naturally, I now have a hard time explaining what we did in seminars, so I instead focus on our current work. But during visits in research institutions, I usually have "lunch with the post-docs" and take that opportunity to delve into "remembrances of things past" where I focus on some take-home lessons.

"Scientists usually collaborate individually and easily based on mutual interest and complementary expertise, and their communication easily crosses borders and cultures."

Still, after all these technological advances, I'm primarily a human geneticist and what still appeals most to me is to look at the human phenotype, try to understand what it is telling us about the function that is lost, and take it from there. For example, there is a disease called A-T-like disease, perhaps the most similar disease to A-T that is *not* caused by *ATM* mutations. The causative mutations are in the gene encoding the MRE11 protein, a component of the MRN complex, a critical player in the response to DNA double-strand breaks. In the early 2000s, we were pondering over the question why these diseases are so similar despite the extremely different nature of the proteins encoded by the responsible genes. A wonderful hypothesis came from a graduate student in the laboratory, Tamar Uziel. By the way, in my mind, the happiest moment in science is not when your own idea turns out to be true, but when your student comes up with a brilliant idea that turns out to be true. Tamar said to me, "I know what the problem of A-T-like disease patients is and

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why their disease is so similar to A-T. Their *ATM* gene and protein are fine, but they cannot activate their ATM protein properly following induction of DNA damage because the MRM complex is required for ATM activation."

ER: That was her hypothesis?

YS: It was entirely Tamar's idea. She went back to her bench and sure enough, her idea was correct. At first, it was somewhat difficult to convince the field to accept this idea since the MRN complex had been known as an ATM target, that is, placed downstream of ATM in a traditional signaling scheme, while we claimed it was upstream of ATM. We now know that many damage response cycles are based on cyclic amplification, which explains this apparent contradiction. Tamar's *The EMBO Journal* paper was followed by a flurry of papers from other laboratories confirming her hypothesis and findings. The take-home lesson? If you believe your data, stand behind them.

ER: I would like to switch gears a little bit to research integrity, which is an increasingly important topic. What is Israel doing in that regard to preserve research integrity and prevent fraud?

YS: I'm not sure to what extent regulatory or inspection mechanisms are developed here at the levels of government or funding agencies. To me as group head, this is probably the worst nightmare, but I've always had full confidence in my team members. We have a self-regulatory mechanism in the laboratory that provides a kind of safety belt: it's the laboratory's culture of taking a critical look at data, especially the exciting ones. This culture is constantly maintained by Yael Ziv, and the students and postdocs quickly adopt this culture. When I accept to review a paper, I select several team members who read the manuscript and we then have a meeting in which everybody makes comments while I take notes. The final review reflects this discussion and is clearly far better than what I could produce without it. People who work on the bench often spot things that may escape the attention of the person in the corner office. Obviously, this is extremely educational for them. But during these enlightening discussions, I sometimes have to say, "Hey, please don't be *sooo* critical!"

ER: Is being so critical typical of Israeli students?

YS: I guess this has to do with the Israeli culture. People are opinionated. You may know the joke that every person here is a political party. And, people here say what's on their mind. All in all, it's for the good.

ER: Do you think this is one reason why Israel is such a prominent country in research, although it's quite small in population and size?

YS: This country has enormous talent and a passion for discoveries and doing something new. One of the sad things is that there is a huge brain drain, because the country is too small to offer enough positions in science. As a result, in many major American universities, you often hear Hebrew in the hallways. I served for a long time on the search committee for new PIs for our medical school. We can offer one or two positions a year and typically select the winner(s) out of 40-50 applicants, many of whom are truly excellent. It's heart-breaking to choose only one or two from these excellent people, and we know that many of them will stay abroad. By the way, after we cloned the *ATM* gene, I had three offers for positions at first-rate American universities, but responded that I was committed to staying in Israel. Other than the obvious "life reasons"— primarily family—I felt that my research environment was excellent and I also owed a lot to Tel Aviv University. On my first day here, the Dean said to me, "I'm rolling out the red carpet for you—but don't disappoint us!" The hunt for the A-T gene was long and arduous, but Tel Aviv University supported me in this high-risk adventure. I owe a lot to this great institution.

ER: What do you think about collaboration with other Middle Eastern countries that are investing into science, such as Saudi Arabia, Jordan or The Emirates?

YS: Scientists usually collaborate individually and easily based on mutual interest and complementary expertise, and their communication easily crosses borders and cultures. On many occasions, I have met with a European, Chinese, American, or Japanese colleague, we quickly discovered common interests and have taken it from there. We cannot deny, however, that conflicts between nations affect scientific communication. I for one would be delighted to collaborate with scientists in the neighboring countries and the Palestinian Territories, despite the complex political situation in our region. I "cast my bread upon the waters" twice in this regard, but unfortunately got no response, for reasons I could understand.

ER: You mentioned to us that your work as human geneticist influenced your social and political views. What's the connection?

YS: I look at human genomes and I see sequences, epigenetic marks, and gene expression regulatory mechanisms that make us all humans. On the other hand, the enormous genetic variability makes each human individual a unique entity, with its own combination of physical and mental traits, capabilities, talents, and personal orientation. I'm a bit deterministic in this regard: I think that most of our basic qualities and traits are determined within our chromatin. As a geneticist this makes you better understand, accept and respect what unites us as human beings and at the same time makes us so different from each other. This recognition strengthened my beliefs in human rights, democracy, and the importance of civil rights and civil rights movements. I had always been in that political domain because this is the way I was brought up and this is how my political thinking took shape already at high school, but at some point, it dawned on me that my choice of profession gave all this another dimension and reassurance. Needless to say, we're now witnessing difficult times for these values. Perhaps, if everybody knew genetics our world might be a somewhat better place to live.

ER: Do you see in Israel also anti-science movements such as the anti-vaccine movement, homeopathy, radical animal rights activists or opposition to genetically modified crops?

YS: These are very different issues, which I would not put together under one umbrella of "anti-science movements". The anti-vaccine movement is a serious threat to human health and welfare. The problem is that in order to explain to people what vaccines do, you first need to teach them immunology. But teaching everybody immunology at an undergraduate level is not feasible. Going back to what I said about everybody knowing genetics, perhaps we should add immunology to the list, or in short, biology—enabling everybody to better understand life on earth—but this remains wishful thinking.

As for homeopathy or any method of alternative medicine, these practices should not be delegitimized. They can live side by side with mainstream medicine and should be investigated using scientific methods and assessed according to their outcomes. Clearly, though,

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homeopathic doctors should be obliged to take the Hippocratic Oath.

"Clearly, science is facing a huge problem these days with decision makers who don't believe in it."

The animals' rights movements are a different story again. These are not simply anti-science movements but people motivated by ideals, who care about animals and devote time, resources and efforts to the cause. Of course, the violence they sometimes express is not legitimate. My approach as a scientist who uses mice for research would be to meet these activists, listen and explain what we do and what our methods are, and try to convince them that research with animals is often irreplaceable. There should be a dialogue. I should mention that we've come a long way with regard to regulation of animal-based research, and perhaps there's still room for improvement. As for the growing dissent against the treatment and often cruel handling of farm animals that provide much of our food—I identify with that wholeheartedly.

As for genetically modified crops, this is an inevitable part of technological progress and is only for the good of mankind. I can, however, understand the concerns, which again are based on lack of information and understanding of the technology. And again, it's a matter of education and dissemination of accurate information.

ER: You are also dealing with ideologues who are completely shut off from reality.

YS: I admit I'm at loss of how to relate to people who are not willing to understand how science works and the basic principles of our work: the pursuit of knowledge, total freedom of thought, of creative activity and expression, rationalism, empiricism, critical thinking, the continuous questioning of existing concepts and dogmas. These should *not* be hard to explain, as opposed to the details of a specific scientific field. But without readiness to listen, we can't go very far. This is one of the reasons I attribute such importance to lectures to broad audiences out of academia. Clearly, science is facing a huge problem these days with decision makers who don't believe in it.

ER: Even in Israel?

YS: Yes, there are communities here that don't appreciate science, and their influence goes all the way to the top of our political system.

ER: I thought Israel was one of the most enlightened societies in terms of science?

YS: We have a bustling, first-rate scientific community. As in many countries these days, some politicians do appreciate the economic wealth coming from technological inventions and hi-tech industries, but that's an opportunistic and narrow view of science. What is needed is appreciation of the foundations of science, most importantly academic freedom and the liberty to think and express your thoughts. Technological advances do not come without basic research, and basic research relies on these foundations. I should stress that all this applies to social sciences, art, and the humanities as well, and perhaps they should have a priority these days in terms of support. You might be surprised if I tell you that if I became president of an academic institution, I would focus first on fostering the humanities. These are the foundations that precede the natural sciences. After all, my PhD degree is "Doctor in Philosophy".

I believe that the foundations of all the decisions I told you about are not in the laboratory but rather in that realm, going all the way back to my basic education. A few years ago, I gave a public lecture at the Technion in Haifa, where I did undergraduate studies, and I invited my first-grade teacher from elementary school, who is now 92. She was sitting in the first row and I said to the audience, "We have a guest of honor here today. My elementary school teacher who taught me how to read and write". My education began with her and at home, and was further shaped by a group of excellent, enthusiastic and inspiring teachers in our small neighborhood high school. I believe they gave me the basic infrastructure needed to make important decisions later, including in science. I realized, in retrospect, that those decisions did not depend only on the scientific findings; they depended on something that was much deeper, going all the way back there.

ER: Dr Shiloh, thank you very much for the interview.

The interview was conducted by Esther Schnapp and Holger Breithaupt.

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