PHOTO OF ANTHONY MONACO, M.D./PH.D.

A Discussion with Anthony Monaco, President of Tufts University

Brian Wolf

Dr. Anthony Monaco, M.D./Ph.D. is the President of Tufts University and is a distinguished neuroscientist that focused his research on the genetic basis of neurological and psychiatric disorders such as autism, specific language impairments and dyslexia. His research group at Oxford's Wellcome Trust Centre for Human Genetics first identified a gene specifically involved in human speech and language. As the thirteenth President of Tufts University, Dr. Monaco brings his experience as a biomedical researcher to contribute to Tufts' excellence in education, research and greater engagement with society.

During your tenure at Oxford, your research appears to be primarily focused on identifying and characterizing genes involved in complex genetic disorders, such as autism and dyslexia. Can you please elaborate on your research?

Autism and dyslexia are called neurodevelopmental disorders, in which children have problems with the development of social communication (i.e. autism), language or reading. My research group wanted to take an unbiased approach using genetics to study these conditions because we knew that these disorders have strong genetic factors involved in their susceptibility. However, their etiology was a bit of a black box. We wanted to use an unbiased genome-wide approach, which scans the whole genome for variants in genes that increase risk. For example, in the autism field, with the benefit of an international effort, a large number of genes have been identified that encode proteins involved in synaptic connections. Our findings indicate that autistic children may have a deficiency in the connections between neurons, called synapses, which are important in neural processing. Regarding dyslexia, four candidate genes have been identified and my research group focused on one particular gene. Yet, all four genes seem to have a role in the process of neuronal migration. After neurons are born, they migrate to the right level of the cortex. We believe that the genes that we have identified are involved in this process. If you interfere with this process in animal models, neurons go to the wrong level of the cortex and this might interfere with cortical processing. In humans, if neuronal migration is even subtly altered, it may disrupt the development of reading. With respect to language impairment, we did identify one major gene, which is a transcription factor called FOXP2. This has a specific role in severe speech and language disorders. Looking at this gene evolutionarily, it seems to have a role in communication in other species, such as song learning in birds and ultrasonic vocalizations in mice.

How did you come to choose complex genetic disorders as your main research focus?

Starting with my graduate work, I focused on muscular dystrophy and identifying genes related to single gene disorders, for which there is usually one gene and one disease or phenotype. I then worked on the Human Genome Project and helped generate maps and resources for researchers to obtain the entire sequence of the human genome. It then became possible to use new technology, analytical tools and our knowledge of the genome to start to tackle more complex and common disorders in which we thought more than one gene was involved. As a result, a whole new institute, The Wellcome Trust Centre for Human Genetics at the University of Oxford, was initiated in 1995 to house core facilities, investigators with specific clinical cohorts, and genome resources to tackle some of these issues. Returning to my roots of neuroscience, I began to think about which common neurological disorders would be amenable to these genetic approaches. Ultimately, I focused on childhood neurodevelopmental disorders.

Genetic disorders affect individuals across the world and research on this subject is obviously conducted globally. What led you to do your research in England and how did your place of study affect the way in which your research was conducted?

That's an interesting question because I originally went over to England for a two-year fellowship to work with a particular individual, Hans Lehrach, who had just established his laboratory in London. He was proposing a particular strategy that I thought would be a winning approach to map the human genome. After my fellowship ended, I received an offer to start my own laboratory at Oxford, which I accepted. In 1995, I began to use the tools of the human genome to understand common disorders such as

Brian Wolf is Managing Editor of TuftScope.

dyslexia, language impairment, and autism. When I started these studies, it was relatively straightforward to recruit large numbers of families to participate because they were being assessed through the NHS (National Health Service) [Great Britain's publicly funded healthcare system]. Due to the NHS network, we could interest many clinicians in the studies to help us organize the cohorts, which overall consisted of thousands of patients and their families. Using these clinical cohorts and their careful phenotypic assessment, we were able to dissect the genetic susceptibilities. These studies made it difficult for me to leave the UK, because, in order to be successful, I needed these resources and the long-standing collaborations.

In addition, scientific studies have estimated that 90 percent of autism risk is attributable to genetic factors and only 10 percent to non-genetic environmental factors. Do you agree and how has this information affected your research, if at all?

This is the traditional view and we always used this statistic, which is based on twin studies. This type of study examines the rate of autism between identical and non identical twins. However, recently, it has come under scrutiny. I think that it is interesting to look at new data with a fresh eye. The most important thing we have learned about autism so far, from both the twin studies and our identification of susceptibility genes, is that the behavioral outcome is not predetermined. If you have two identical twins with the same genetic makeup and one of them has autism in a severe form, it is not always the case that the second co-twin has severe autism. A significant percentage of the time, they will have a less severe form of autism and, sometimes, they are clinically normal. We conclude that while genes have a large influence on the outcome, there are other factors, which are developmental or environmental, that influence the final phenotypic outcome. The other thing we have learned from the identification of genes involved in autism is that they can have a role in other neurodevelopmental disorders, such as epilepsy, learning disability or schizophrenia. Genes do not encode for clinical diagnoses, but they encode for proteins, which help build the brain correctly. If something goes wrong in neurodevelopment starting from a genetic change, the final behavioral outcome is not always the same due to many other factors. The final result can be variable, whether it is autism, schizophrenia or learning disability. This was a big surprise to us and is not something we would have predicted from the start.

Have there been any practical applications for this research (i.e. early detection of autism)?

Yes, you can screen genes using DNA arrays to search for large deletions or duplications of genetic material in children with autism. This helps us to understand which genes harbor etiologic mutations that may give rise to autism. It can be helpful in a diagnostic situation for younger children in the family, who may or may not have symptoms of autism, and genetic findings can provide some guidance for risk. However, there are ethical issues with this approach because, as I said, these mutations do not always result in autism. For example, there is a concern that you may detect the same genetic change in a younger sibling of an older child in the family who has autism. Therefore, the question arises whether it is ethical to label that younger sibling to be at risk for potential problems if you do not know that the outcome is genetically predetermined. The detection of major DNA changes can be discovered prenatally, but we do not know enough yet about all the genetic factors in autism to offer accurate prenatal tests. It is not a single-gene disorder like cystic fibrosis or muscular dystrophy where you can perform a sensitive and specific prenatal test and provide genetic counseling to the parents. In the case of autism, all you would be able to provide is a risk factor. As we gather more information on susceptibility genes and other factors influencing outcome in autism, this information may be more useful in the diagnostic arena.

Are there distinct similarities or differences in the way medical research is conducted in America and in Great Britain?

One significant difference is that there are many well-developed and structured MD/PhD programs in the US. In terms of getting medical doctors interested in biomedical research as an academic career, the NIH funds these programs very well. In the UK, I believe that Cambridge has one of the only programs that offer a structured MD/PhD degree. For the other medical schools in the UK, most of the doctors obtain their medical degree first and then they have to apply for separate funding to obtain a PhD. It is a more tortuous route to get involved in biomedical research. Other than this discrepancy, I think basic biomedical research in the UK is as strong and productive as it is in the US. This is due to funding from the Medical Research Council, which is government supported. In addition, there are very good biomedical charities, such as the Wellcome Trust, British Heart Foundation and Cancer Research UK, which support research at the same level as government funded research.

As the new president of Tufts University, which includes the School of Medicine and the Friedman school of Nutrition Science and Policy, how do you view Tufts' role in the global health community now and in the foreseeable future?

Tufts has an interesting mix of graduate and professional schools situated in one university. It is rare for a medical school to be aligned with very strong nutrition and veterinary schools and we should take advantage of the opportunities that poses. One of the roles that I am trying to play is to help stimulate and catalyze thinking across the schools in certain thematic areas. For example, we can integrate our activities better for life and health science fields such as neuroscience, cancer, obesity, infectious disease and global health. This is not to say that there are not already many fruitful collaborations between the schools, but I would like to put the activity on a better structural basis. I

also would like to focus on the graduate and undergraduate programs that underpin the research conducted in these thematic areas. I hope that graduate and undergraduate students would be able to move across the schools to different investigators and projects in a more flexible, cross-disciplinary way.

As a scientist and an administrator, is it difficult to find a balance between the two? If so, how do you bridge this gap?

During my time as Pro-Vice-Chancellor at Oxford, I did continue to supervise my laboratory, but at Tufts I am not going to set up a new laboratory. It would interfere with my leadership role as president. Yet, by bringing my knowledge and scientific perspective to the position, I understand the importance of collaboration, openness, and transparency to solve complex problems, rather than trying to do it in a single, solitary laboratory. I think that this approach is relevant to the way in which a university works to solve complex, global problems. We cannot accomplish goals easily if we are separated in each individual discipline. Every discipline has its own limitations in how much progress can be made. By working together other disciplines complement the actions of one another. Only then we can come up with better and more innovative solutions.

Based on your strong Internet presence for Tufts, do you see social media as a vital source of communication in the medical and research field (i.e. the ability to create dialogue between researchers around the world)?

I originally got involved with Twitter because my colleagues in my research field were using it, particularly in the fields of neurodevelopmental disorders, genetics and psychology. Many of my colleagues had started to produce posts on blogs and tweets to broadcast the most recent work in their respective fields. I found it to be an interesting and personal way to keep up with what was going on in my field. In addition to looking through journals to find what is interesting, they were telling me directly what they thought was interesting. I realized quickly that not only could I communicate with people in my own area of expertise but also across different disciplines. Now, as president, I try to communicate with all sectors of the Tufts community, including students, teachers and faculty, using a variety of media as effectively as I can.

What advice would you like to impart to students who wish to embark on a career in the medical research field?

I think medicine is an interesting field because it opens a lot of doors. Not everyone who goes to medical school will then proceed to clinical practice as a life-long career. Individuals will consider roles in research. Others will study for further degrees and some will use their medical degree to work on global health policy or health care delivery or get involved in the biotechnology and pharmaceutical industries. I do think that, like other professions, it expands your opportunities, rather than restricts them to one particular area. Most important, there are many different avenues to take to follow your passion in the field of medicine.