Q & A

Kerry Bloom

Kerry Bloom was born in Washington DC and grew up in Bethesda wondering what this odd government complex was doing out in the suburbs. He gained his first glimpse into science as a high-school student attempting to isolate Salmonella *from the Potomac River under the guidance of Stanley Falkow at Georgetown University. He went to Tulane University where, in addition to listening to Preservation Hall Jazz and never missing a Mardi Gras, he ran polysomes from fly salivary glands on sucrose gradients; then to graduate school at Purdue University where he made cDNA from chick oviducts for studying the chromatin conformation of active genes. To become a card-carrying molecular biologist and learn 'cloning' he went to work with John Carbon at the University of California, Santa Barbara. John and his laboratory had just destroyed one of the first DNA libraries per decree of the NIH, and still managed to identify the first eukaryotic centromere from budding yeast. It took a few years, but Bloom became enamored with yeast as a model organism when he learned how to engineer chromosomes. He went to the University of North Carolina at Chapel Hill, where he has been since 1982. Throughout his career, Bloom has been interested in how molecules (from mRNA and proteins to chromosomes) and larger structures (spindles to nuclei) move in living cells. He is currently trying to bridge modern cell biology with biophysics to understand how the mechanical properties of DNA influence biochemical reactions* in vivo.

What got you interested in biology? I was one of a bevy of pre-meds at Tulane University who thought that any interest in biology meant medicine. My parents were in business and delighted with the prospects of a young Doctor in the family. Unfortunately (for them) I started working in the laboratory of Erik Ellgaard who had done early work on the role of histone acetylation and gene expression with Ulrich Clever at Purdue University. These early experiences and long meanderings at graduate student's homes discussing early embryonic development with the young faculty were thrilling. I was amazed that one could sit around trying to figure out how things work, and call this a job. I was also very mechanically inclined (and have owned and own several old triumph Bonneville motorcycles) and liked the idea of tinkering with something that was alive. Much to my parents chagrin, I applied to both graduate school and medical school. When the medical faculty asked me what I would do if I didn't get into their school, I responded with, "I'll be a motorcycle mechanic, it's the same thing right, plumbing and electricity". Well, this sealed the deal for graduate school and I found a home.

What is the best thing about being a professor at a large research university? The undergraduate students are still by far the most challenging and rewarding. Scientific discovery is a new world for them. We, as seasoned scientists in the field, see how quickly ideas become dogma, then how research is framed by these preconceptions. The beauty of youth is in its naiveté. It is getting harder and harder to find new and different ways of looking at problems, and for undergraduates and new graduate students this is their forte. This is also one of the main reasons to switch fields or approaches. One of our venerable predecessors, D'Arcy Thompson, said: "All our descriptions, all our interpretations, are bound to be influenced by our conception of the mechanism before us: and he who sees threads where another sees channels is likely to tell a different story about neighboring and associated things" (in *On Growth and Form*, 1917). Fresh perspective is as important as deep insight. That said, it is daunting to look into a sea of a couple hundred students who think you know something about biology. It is exhilarating to think that you might turn a few on to the secrets of life.

Who are your scientific heroes? One of the major tools in my current research is dicentric chromosomes. It turns out that this is a wonderful tool for doing biophysics *in vivo*. Barbara McClintock was the first to describe the biological consequences of a dicentric chromosome, before the discovery of DNA. To this day, I cannot fathom how she made the leap from mottled corn to dicentric chromosome breakage–fusion–bridge. She was so far ahead of her time that few in the field could understand her papers. It takes true passion to work on something for which you receive very little positive reinforcement, and for this reason she continues to be a source of inspiration.

Bruce Nicklas is a *bona fide* pioneer in the biophysical analysis of chromosomes. With his microneedle in hand and grasshoppers from the field, he pushed and pulled chromosomes and figured out how much force is required in mitosis. His estimates of force in the spindle in the mid 60s are still the best in the field. The more I learn biophysics the greater I appreciate the impact of his early explorations. Luckily for me, he is still active in his office at Duke University, and listens and nicely tells me when I'm on or (more often) off track.

In the world of molecular biology my postdoctoral advisor John Carbon embarked on a journey to isolate centromeres. John leads by example. At his 70th birthday celebration, he was to give a presentation of the paper he was most proud of. You can imagine the former postdoctoral fellows sitting in the audience hoping their paper to be the one. In typical Carbon fashion, he chose to discuss a chemical synthesis he was particularly proud of, in German no less. There were many sayings posted around their laboratory, one of the memorable ones "would John Carbon do this experiment?" John believed that it was just as hard to do an important experiment, as it was to do an irrelevant one. To this day I ask myself, would John do this experiment? John was also the one who taught me about controls. You cannot do every control; the key is knowing the right one.

Finally, Ted Salmon with his mentor Shinya Inoue: these two men understand light in a way that I can only describe as 'Einsteinian'. To see

Ted demonstrating the particle and wave motion of light as he dances across a room is to know that I can never understand light like he does. But Ted has taught me (and many others) how to use light to study cells. He is also one of the more nurturing personalities in the field. We give a lot of credit for the use of GFP revolutionizing cell biology, but in fact it is the deep understanding of light that allows us to peer into the inner workings of cells in such a serious way.

How (and why) did you get into biophysics? In spite of my best plans — and attempts to think like John Carbon — I follow experiments rather than a grand plan. We had been using GFP to image chromosomes in live cells and found that our dicentric chromosome could stretch to its B-DNA length in living cells under certain conditions. Moreover, the DNA would periodically break and recoil. The recoil was qualitatively similar to recoil of naked DNA in early flow experiments performed by several notable physicists. The papers describing DNA under flow were written in the language of polymer physics, with equations rather than words. Thus, I started my foray into biophysics. The turning point was the discovery of "The New Science of Strong Materials, or why you don't fall through the floor" by J.E. Gordon in 1968. It is written in novel form and describes the mechanical properties of materials, why we need to worry about them, how to quantify the physical properties of a substance, and intuitive ways of thinking about how to build a machine (for example, a mitotic spindle). A little understanding of language can be dangerous and we have started applying these physical concepts to our experiments. I feel like a child in a sandbox, there is a whole new world out there to explore.

Why is it important to talk to physicists? The revolution that was begun with cloning gave us the genome and now the (more or less) complete parts list of the cell. The biologists are finally ready for the physicists. It turns out that another famous figure saw this revolution coming. Richard Feynman, in one of his lectures in 1959 "There's Plenty of Room at the Bottom", realized that our intuition fails us inside the cell. The key parameter is Reynold's number (R_e), the relation between viscous and inertial forces. Our world ($R_e > 1$) is dominated by inertia, while the cell ($R_e <<< 1$) is dominated by viscosity. in the world of a cell, if you take a nut off its bolt, it doesn't fall off. Paraphrasing his lecture, Feynman told us that the game is not 'two-hybrid' but how the myriad of non-productive interactions are prevented from mucking things up. When A dissociates from B, they stay together until another force drags or pulls them away from each other. It's easy to imagine how microtubule subunits add on the plus-end while the plus-end is at a kinetochore or the cell cortex, because at low R_e large molecules just don't float away.

In addition to the physicists, the other tool that has come of age for biologists is molecular modeling. Modeling is not burdened by intuition. If done right, modeling provides a powerful tool to help guide experiments. For me, a model is just another tool to help design an experiment, especially in the world of low R_e. We need to be able to explore the biology with the model by tweaking the equations to give some outcome, and testing how well the predicted outcome matches the experimental situation. The problem with any new toy is that it is not infallible. One can model anything, but a useful model for a biologist is one that will make discrete predictions that can be tested and refined in an iterative way.

How has the culture of science changed since you began your career? When I was a graduate student, one laboratory was its own kingdom. That is rapidly changing. Not only because of the internet, but many of the technological advances — in microarrays, microscopy, mass spectroscopy, mathematical modeling — preclude any given laboratory from 'doing it all'. This specialization in technology is a benefit to scientific discovery, but a disadvantage to an individual crossing disciplines. Now the challenges are not to just find collaborators, but to learn new languages, new approaches and new ways of thinking.

How should we teach the next generation? We should start by not teaching facts. We should teach process. We should teach uncertainty, we should teach joy in discovering something we don't understand. It drives me crazy when a student comes into my office saying, "the experiment didn't work", when a result was totally unexpected. This teaching paradigm exists and it is taught each summer at several research stations, most notably at the Marine Biological Laboratory in Woods Hole, MA. The Physiology Course is over 100 years old. It reinvents itself every five years, with the intent to get some of the best and brightest scientists who practice innovative approaches to basic problems in biology — to teach the 'approach du jour'. What are the key questions in the field, how do we get to the key issue pretending we have every technique and instrument at one's disposal. Note they don't teach facts, they teach questions, process and strategy. This is how you excite the next generation. Look at all the phenomenology we don't understand, and all the questions we need you (new students) to help us discover.

What suggestions do you have for young scientists looking for jobs? Collegiality — science is not the most nurturing profession. Your paper will be rejected. Your grant will be rejected. You will not be asked to Chair a session at the Gordon conference, but your archenemy will. So how do you deal with this as a young professional? The colleagues at your institution are your family. They are the ones that you see day in and day out and tell you that you're great. They'll read your grants and papers, and if they're good, they'll tell you the truth, but nicely. You want to find an institution with a supportive rather than competitive culture.

What are the challenges for the future? The genome is done. The public perception is that we just need to link each disease to a gene, fix the gene and done. I understand why we've worked so hard to educate the public about the genome, but now we need to begin discussions to inform the

public that the parts list doesn't give us the key to life. The genome initiative has taught us the value of sharing. We need to learn this lesson. Cell biologists are generating huge data sets. As one peruses the poster sessions at any major meeting, it is inescapable that more data are being generated than a single person or even small laboratory can fully analyse. Each investigator typically analyses one or two aspects of their own data set. It would be interesting if one could download (for example) images of fluorescent chromosome spots in mitosis from a laboratory that has the images and apply their analysis tools. While this may seem a bit heretical, this is exactly where the genome was circa 1975. An investigator would not dream of sending their sequence to a colleague before publication. And don't we all remember attending meetings and being frustrated when a colleague would not disclose the gene name? (Colleagues were very protective of their A, G, C, and T's just a decade ago). While the data sharing model opens up a Pandora's Box of questions, this is the direction things are going. There are laboratories that are great at imaging and others that are great at analysis. Wouldn't it be wonderful to create a web site, like the genome sites, where investigators with analytical skill sets could go for data! Unlike the genomes, image sets are not strings of AGCT, but 0's and 1's in different formats, time scales and operating systems. We should think of the cell biologist's data set as an 'imaginome', figure out how to share these data sets in the spirit of the genome world and develop strategies for the developers of analysis tools to have free reign of a reliable database. Physicists, mathematicians, astronomers, engineers, and computer scientists have amazing ways of analyzing digital data and pulling out patterns from complex arrays. Let's figure out how to pool resources for the next generation to explore.

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Book review

The dog: a biologist's best friend

Brian Hare

Dog behaviour, evolution and cognition — Adam Miklosi. Oxford University Press, Oxford, UK, 2008. ISBN 978-0-19-929585-2

In your interactions with dogs you have likely wondered: do dogs recognize each other and different people? How sensitive is a dog's nose and what is their vision like? How good are dogs at finding their way home? What can a dog learn from another dog? Do dogs know what you are trying to say? Do they know what you are thinking? When did dogs start living with humans and why? Where did dogs originate? What are the differences between breeds? Whether one is a behavior geneticist, a population biologist, a psychologist, an anthropologist or just a dog lover, you cannot help but wonder about the lives of dogs and our lives together with them. But even though Darwin began the *Origin of Species* with examples of dog domestication, and Pavlov's dogs were the first to reveal to us classical conditioning, until now there has been no place to obtain answers to questions such as these that are based on rigorous scientific research. Adam Miklosi's new book aims to fill this gap and will be a landmark contribution to the study of animal behaviour, evolution and cognition. Over the past decade there has been an explosion of interest in dogs and it is this work that Miklosi uses to provide us with the first modern scholarly review of all there is to know about dogs — and the first review of scientific research on dogs since Scott and Fuller's pioneering book *Genetics and Social Behavior of Dogs* published in 1974.

Miklosi himself has been at the center of the surge in research interest on dogs over the past decade. So there is no one in a better position to write the first modern review of dog behavior, cognition and evolution. He has played a leading role in the work of the largest research laboratory working exclusively on dog behavior and cognition, at Eotvos University in Budapest, Hungary. In many ways this book is also a tribute to the hard work of his colleagues. Miklosi and his team have published scores of empirical papers on all aspects of dog behavior and cognition that test phylogenetic, ontogenetic, and even functional explantions of behavior. All of the best experimental work starts with careful observation of the population or species under study. Miklosi and colleagues have taken this dual approach to their own work with dogs. In some cases they have gone to extremes to understand dog behavior before they attempt to tease apart the mechanisms that guide the behavior they observe. As an example, Miklosi and colleagues dedicated countless hours to personally raising a group of wolf and dog pups in identical rearing environments to allow powerful direct comparisons. They have studied the behavior of hundreds of dogs from dozens of breeds in dozens of different cutting-edge tasks that they developed specifically for examining dogs. This means for the first time you will find in this book a review by a dog expert who is explaining their behavior and cognitive skills through the lens of a careful observer and scientist, as opposed to a dog trainer or untrained enthusiast.

Miklosi's review is authoritative and exhaustive. The book is organized into eleven chapters covering the very latest research findings and are chock full of fun facts. For example, did you know the wolf was the smallest of eleven related predators at the time it first evolved? Or that dogs can see yellow and blue but not red and green. The first two chapters discuss the history of dog research and conceptual and methodological issues regarding the study of behavior in any species. The next eight chapters each focus on a theme, including: dogs in human society; dogs in comparison to other canids; the genetic and archaeological evidence for domestication; the perceptual world of dogs; dog cognition regarding the physical world; dog social cognition; behavioral development in dogs; and temperament and personality in dogs. No other author has attempted to review such a range of topics about dogs in one volume. One of the major devices that Miklosi uses to succeed are break out boxes; these include additional illustrations, original figures and detailed explanations that allow