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Of Mice and Men, and Medicine: an interview with Monica Justice

Monica Justice, a recently appointed Senior Editor on *Disease Models & Mechanisms* (DMM), is Professor in the Department of Molecular and Human Genetics at Baylor College of Medicine (BCM). She leads several research teams that are merging mouse modeling with clinical genetics to elicit new information on disease mechanisms and to develop potential treatment strategies, with a focus on hematopoietic cancers and genetic syndromes. In this interview, Monica discusses what led her to focus on molecular, developmental and translational biology; her current work and future goals; and the reality of creating a balance between a demanding research role and life beyond the lab.

Monica Justice was born in western Kansas and spent her early years on the family farm, which inspired an enduring interest in biology and animal genetics. After working as a medical technologist for 6 years following her bachelor's degree, she returned to graduate school (Kansas State University) to undertake a PhD in developmental genetics. During this time, she helped to pioneer chemical mutagenesis approaches in mice. Subsequently, she was a postdoctoral fellow in the Mammalian Genetics Laboratory at the National Cancer Institute (NCI), the laboratory that created the mouse-human comparative molecular map, with Drs Neal Copeland and Nancy Jenkins. Now based at the Baylor College of Medicine, Monica's research exploits the remarkable conservation in genes and whole chromosome regions between the mouse and human. Her overall research goal is to merge mouse modeling with clinical genetics to understand the basis of and develop treatments for human diseases. The internationally recognized program that she leads at Baylor has generated hundreds of new mouse models of human disease, which have enabled discoveries of gene functions in diverse areas, including cancer, reproduction, neurobiology, obesity, and blood, heart and bone development.

Can you pinpoint what made you decide to embark on a career in science?

My fascination with biology seems to be ingrained; my early interest in cattle and animal genetics was passed down to me from my grandfather, who was a veterinarian and cattle rancher. I initially also wanted to be a veterinarian, but later realized I had an overwhelming need to help people. I was convinced that my future path should be directed towards improving human health, primarily in the field of childhood diseases, and I planned to go to medical school. On taking a post as a medical technologist after my bachelor's degree in science, I had the opportunity to work with children who were affected by cystic fibrosis and leukemia. This was an invaluable experience because it made me admit to myself that I found it too easy to become emotionally involved to be an objective physician. My career path became clear – it was to be graduate school rather than medical school, but my focus on pediatric medicine has stayed with me.

Looking back on your career, are you surprised by the path you have taken?

My goals have often been changed by situations. In graduate school, I was pursuing a degree in microbiology and immunology, and my first professor, Vernon Bode, taught a course called 'Genetics of Microorganisms.' Vernon was a lambda phage geneticist who was in the process of switching to mouse genetics. He convinced me that the mouse was the next big model organism and talked me into joining his lab. Being his first graduate student to work on mice was an unexpected change in direction, which was the foundation of my career.

Who have been your most important mentors?

Vernon Bode and my postdoctoral fellow mentors, obviously, but after that it becomes

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difficult to list all of the people who have motivated and inspired me. Those who have influenced me particularly are probably Ian Jackson of the Medical Research Council Human Genetics Unit in Edinburgh, Scotland, Miriam Meisler of the University of Michigan Ann Arbor, Bruce Beutler – winner of the 2011 Nobel Prize in Medicine – now at University of Texas Southwestern Medical School and, of course, Allan Bradley at Baylor [see below].

How did your first postdoc, at the Frederick Cancer Research and Development Center at NCI, shape your thinking?

At the time that I chose NCI to do my postdoc, molecular biology was a revolutionary new field for mouse genetics. Neal Copeland and Nancy Jenkins were the leaders in that area at the time, and I was lucky enough to be accepted into their group. So, my postdoc really led me into mammalian molecular genetics and I have never left this area.

How long have you been at Baylor College of Medicine in Houston?

2013 is my 15th year at BCM. In the late 1990s, I was developing high-throughput methods for assigning functions to mammalian genes using unique genetic strategies at Oak Ridge National Laboratory, but various factors meant that it was right to move on. I had been collaborating with Allan Bradley (now leader of the Mouse Genomics Team at The Wellcome Trust Sanger Institute, Cambridge, UK) who was already at BCM. We had just written and received a large program project grant to use the first mouse balancer chromosomes in a saturation mutagenesis screen. At that time, Allan had already been developing methods for engineering whole mouse chromosomes using Cre-*lox*P technology.

And what made you move to BCM?

Allan convinced me to interview at Baylor, although I thought that I would never move to Houston, Texas! But it was clear that the Department of Molecular and Human Genetics was very stable, and I was pleasantly surprised by the city. I accepted the position, moving to Baylor just after the start of the project grant, and have had few regrets. My move is now easily justified, as Houston was just voted the 'coolest city in America'!

What has been the essence of your research strategy at BCM and how have you made a difference to the mouse genetics program there?

My research has consistently exploited the fact that genes and whole chromosome regions are conserved between mouse and human. In my first collaborative project with Allan, our plan was to assign functions to mouse genes and, in doing so, suggest the function of the corresponding human genes. We decided to focus on the genes on human chromosome 17; these all lie on the distal portion of mouse chromosome 11, making it the most conserved autosome between the two species. Just as Allan was convincing Art Beaudet to recruit me to Baylor, the ground was being broken to start building a new mouse facility. This gave me the opportunity to help design and shape the plans to incorporate a mouse behavior-testing suite in addition to numerous procedure rooms for assessing many mouse phenotypes.

What research milestones have you achieved at BCM?

A big early 'win' was that Allan's chromosome engineering strategy allowed us to generate balancer chromosomes in the mouse for the first time. We went on to design and generate inversions in various regions of the genome, tagging the inversion with a mouse coat color gene. This genetic strategy led to the efficient isolation of a multitude of mouse mutations. Three of my postdoctoral fellows (who contributed to the isolation of mutations, complementation testing, their characterization and their molecular identification) were co-first authors when the work was published in *Nature*, and the work has spawned a multitude of publications and ongoing projects.

This project revealed how little we know about mammalian gene function, and the only way to go from there was up… Since its inception, our internationally recognized program has created hundreds of new mouse models, enabling discoveries of gene function in diverse areas such as reproduction, neurobiology, obesity, metabolism, and blood, heart and bone development. We have also established many mouse phenotyping methods; these efforts have driven the field forward in a short time, ultimately laying the groundwork for Phase Two of the International Knockout Mouse Project, KOMP2.

What is your greatest scientific achievement to date?

Until recently, our group's mouse ENU mutagenesis project was our most significant research accomplishment. Our group continues to lead the field, and we're now applying NextGen sequencing methods to efficiently identify ENU-induced mutations. In addition, we're still generating novel models of human disease in the KOMP2 project. We have shown in these projects how new technologies can be applied to old problems to change the way genetic experiments are carried out in mammals. I say "until recently", though, because I think that project might soon be eclipsed by our discovery of a pathway that can be targeted to treat human disease, particularly Rett syndrome, a finding we've uncovered using mouse genetics as a tool. These findings will be published in 2013-2014 and beyond, so time will tell.

How do you maintain your personal focus and motivation when research problems seem particularly difficult?

It's vital to be able to accept that you are wrong. I have seen people so focused on their favorite hypothesis that they can't move forward. When the data show that you have chosen the wrong direction, it is best to accept it, formulate new hypotheses and move forward.

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What is your current role with DMM?

I accepted Vivian Siegel's invitation to be on DMM's editorial board some years ago, and I was more than happy to accept the position as a Senior Editor from the beginning of 2013. I believe in the journal because it has a unique niche, one that is set to expand as new models of disease are increasingly used for preclinical trials for new drugs.

What do you feel is the main benefit of DMM in this field of science?

DMM is unique. It not only promotes disease models in a wide range of model organisms – including yeast, worms, zebrafish, flies, mice,

rats, dogs and non-human primates – it also brings academia and industry together in an unusually happy marriage. DMM is becoming a resource for scientists in diverse communities, and is perfectly placed to support these communities in the way that we expect they will develop. In the past, model organism work has focused on understanding the basis of disease and on generating the models. DMM will provide a home for the publication of ground-breaking research that goes a step further, and uses models to identify methods to ameliorate human disease. This is certainly one of the goals of our group in the near future, so I think becoming a Senior Editor at DMM is a perfectly timed opportunity to encourage this area of research to flourish.

What would you like to achieve in the next decade?

We have three primary projects, each of them relevant to my role on DMM: cancer genetics (focusing on leukemia), suppression of the symptoms of genetic disease and phase two of the knockout mouse project (KOMP2).

In the leukemia project, I would like to target and eliminate cancer-initiating cells in tumors entirely. I believe we are well on our way, and are focusing on the *PRDM14* oncogene, encoding a pluripotency factor. This project has already generated a new type of mouse model that will be used to find methods for eliminating these initiating cells. However, it is relatively early in the project; we need to look at the data, get some publications out and have a lot more discussion before we can determine the full potential of this approach.

A second major focus of my current research is to use genetics to uncover treatments for diseases such as Rett syndrome, which were previously considered untreatable. Funded by the Rett Syndrome Research Trust (RSRT), we are using a genetic suppressor screen in the mouse to uncover pathways in disease pathogenesis that could be drug targets. RSRT has just funded an ongoing saturation screen in this area. Our goal is to identify all pathways that lead to symptoms caused by mutation of *MECP2* (the affected gene in Rett syndrome), and to inform the community as to which of these pathways can be targeted for drug discovery.

I hope that KOMP2 continues to generate valuable mouse models of human diseases, but I want it to do much more. It has the potential to change the current environment of mouse work, providing guidelines for standardized broad-based mouse phenotyping and quality control measures. I would like to develop mouse models as preclinical tools that can be used for preliminary testing of potential human disease treatments.

How do you relax and have fun away from the lab?

I have too many hobbies – including gardening, reading, playing the piano and exercising – but my favorite thing to do to relax after a stressful day is to cook. My family loves this, but thinks it is a funny way to relax. I believe that most molecular biologists make good cooks.

Is there anything that people would be surprised to learn about you?

That I am a breast cancer survivor; I was treated successfully more than 21 years ago, and my experience has had a profound impact on my attitude to life both in the lab and in the wider world.

DMM greatly appreciates Monica Justice's willingness to share her unique thoughts and experiences. She was interviewed by Kathryn Senior, Freelance Science and Medical Writer. This piece has been edited and condensed with approval from the interviewee.