Bench to bedside with fruit flies: an interview with Ross Cagan

Ross Cagan, new Editor-in-Chief of *Disease Models & Mechanisms* (DMM), is a developmental and translational biology researcher with expertise in using fruit fly models. Based at the Icahn School of Medicine at Mount Sinai, he holds professorships in Developmental and Regenerative Biology, Oncological Sciences and Ophthalmology. He is also Associate Dean of the Graduate School for Biological Sciences and co-founder of Medros, Inc. In this interview, he recalls the events and mentors that helped shape his career, explains why he loves flies, and outlines his vision for DMM.

Ross Cagan was born in Trenton, New Jersey in 1960. After completing his undergraduate studies in biology at the University of Chicago, he undertook a PhD in Neurobiology at Princeton University, under the supervision of Donald Ready. His graduate work and the mentors he encountered early in his research career inspired an enduring interest in fruit flies as a simple and effective model to study aspects of development. Following post-doctoral training at UCLA, Ross moved on to Washington University in 1993, where he headed a basic research laboratory for 14 years. During this time, the lab's focus shifted from eye development to cancer and metabolic disease, which motivated his move to Mount Sinai Medical Center in 2007. Taking advantage of the many tools available for translational biologists at Mount Sinai, the group is now focusing almost exclusively on using *Drosophila* models to accelerate drug discovery for the treatment of cancer, diabetes and other chronic diseases. In addition to the many significant contributions that Ross has made to the fields of eye development and metabolic disease during his career to date, he has also trained over thirty scientists, and his role as mentor and educator is one that he finds stimulating and immensely rewarding.

Did you always want to be a scientist?

I've loved science since I was a kid, but I actually started as a musician at the University of Chicago. My band was none too successful; science seemed a better option and in some ways more subversive.

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

My Dad is fond of saying that the secret to success is showing up, and I do like to work hard at things that I consider important. Early in my career I was busy studying, learning and increasing my skills and experience, yet my focus was short term: "let's get the next thing done". I only started to gain a true career vision of where I wanted to go scientifically once I was tenured. My kids were older by then, giving me the chance to refocus and think more broadly. So, about 5 years ago I changed the focus of my lab from development to disease. It was a good move; I find change to be very positive. I'm sometimes surprised at how conservative and specialized we scientists tend to be; it seems counterintuitive to me since our job is to explore and to challenge dogma. I like Seymour Benzer's idea that a scientist should switch fields every 10 years.

Which key people in your field influenced you?

I'm continually surprised and grateful that great scientists have taken the time to help me advance my career over the years. As a young graduate, my PhD advisor Don Ready made science fun. Yes, it's hard work and it can be frustrating but the fun part of science really is underrated. Another key mentor was my first chairman Jeff Gordon, who understood the importance of being a cheerleader and who taught me about leadership by example. Eric Weischaus at Princeton and, more recently, Sam Wells have also inspired me. They both have the sort of character that's worth emulating, so I'm always watching them and taking notes.

You moved around quite a bit during your training and early career, from the University of Chicago to Princeton to UCLA – what stimulated your choices of institution during that time?

Strictly science. It sounds obvious with the benefit of hindsight, but when I was at the

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University of Chicago, Haig Keshishian (then a postdoc, now a Yale professor) told me that molecular cloning was going to be big and that I should find a genetic system to take advantage of it. This was a key piece of advice.

I settled on fruit flies as my model of choice. I love flies! They are quick and easy to manipulate and provide a simple model with the tools to study development and disease. Don Ready at Princeton seemed a good fit and the money was good – we made US$7500 a year – so everything came together. I moved to UCLA as a postdoc with Larry Zipurski to take the fly and 'go molecular'. Again a good choice: Larry was great to work with due to his professionalism, drive and calm demeanour.

How long did you spend at Washington University School of Medicine and how did that help shape your research focus?
14 years. I really grew up as a scientist there – Washington University is a great place to start a career. My wife is also a scientist and being in such a family-friendly environment that retains high-level science was absolutely critical because it enabled us to flourish in our careers and to enjoy being parents and raising our two girls. We are very close as a family, although our girls are undoubtedly sick of hearing us talk science!

Why did the move to Mount Sinai come about?
Although the stability at Washington University was crucial to that phase of my life, in 2005-2006 I realized I was getting lost in the day-to-day routines and I needed a new environment to snap me out of that. Mount Sinai is a young, growing institute with a clear view of where it is going and this move was key to stimulating me to rethink my approach to science. Mount Sinai and also New York City really promote innovative, bold thinking. Most of our friends would agree: my wife and I are fish in water here.

Tell us a little more about this sea-change in your thinking.
The move to Mount Sinai brought about a very significant change in the way my lab was working. Until that point we were focused almost exclusively on basic research into development. In one fell swoop, we changed that to concentrate, almost exclusively, on translational research with the aim of developing therapeutics for cancer and chronic diseases such as diabetes.

Fruit flies are arguably the simplest model system for studying solid tumors. They have epithelia that behave like human epithelia, they have a short lifespan and a dizzying array of off-the-shelf tools to get started. The goal of using them in translational research is to generate a new therapy, one that works in patients. This aim impacts our approach at many levels. While we think hard about mechanisms, we are always thinking of the bigger picture too – the avenue forward to therapeutics. Sometimes the two endpoints are aligned, sometimes not. A therapeutic goal is a hard taskmaster – you know when you are going off-track because you end up with something that doesn't work in a patient.

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I love my current group: they are smart, independent and ambitious (even if they are worried about the future). We are moving from mechanism to therapeutics to personalized medicine. I am excited about the possibility of weaving these three strands together, and this is an important part of our vision for DMM.

How close are we to being able to offer truly personalized medicine?
We are still in the early stages but it's no longer a far-off dream. My laboratory has begun working with samples from individual patients, doing whole exome and whole genome sequencing, RNA-Seq deep sequencing, and creating PDX [patient-derived xenograft] mouse models, fly models and cell culture systems, all geared towards drug screening and drug development. Our goal is to identify drug cocktails that benefit individual patients.

We've started with patients with head and neck cancer – they have the timescale to be able to benefit from this approach. To expand our efforts to more aggressive tumors, we are working to speed up the scientific steps required: in addition to getting the science correct, the oncologists, pathologists, bioinformaticians and the whole clinical team need to work together in a smooth continuum. I'm finding that building the infrastructure requires as much effort to crack as the science; another opportunity to grow as a scientist. With the help of people such as Eric Schadt and Marshall Posner, the infrastructure and people required are now coming together, and therapeutic opportunities will undoubtedly follow.

You've said you love flies, but are they the best model of human disease?
Just as an illustration, one of the 'crazier' projects we are working on at the moment is diabetes. Even with my years of experience with flies I am still amazed that if we feed fruit flies a 'bad' high-sugar diet (bananas), they develop diabetes, just like we do. Their hearts and kidneys fail, mirroring human diabetic cardiomyopathy and nephropathy. We can also model diabetes with cancer – and these results are as worrying as they are intriguing. Flies with cancer that are fed on bananas to make them diabetic show accelerated tumor growth and a higher number of metastases. This again mirrors human disease and presents a great opportunity to work out the pathways involved and to develop therapeutics to treat cancer in diabetic patients.

What is your greatest scientific achievement to date?
Speaking strictly scientifically, a major achievement has been to show that flies can be effective in developing real world therapeutics. Personally, I find my role in training the most gratifying; my mentors showed me the fun of science and I would consider it a huge success if I was able to impart this to others both in my lab and in my company. It can be frustrating to see good people leave once they have become a part of your team, but it's also important to remember that this is really our role. New trainees provide the lab with fresh approaches and new ideas, while we as PIs give young scientists a springboard to build the career they want.

What would you like to achieve in the next decade?
I am grateful for the opportunities Mount Sinai has given me and I'm looking to execute some long-term initiatives. I have two major goals: the first is to push forward our efforts at achieving personalized

medicine, but the second concerns science education. If the scientific enterprise is to continue to grow, it likely won't be through government-sponsored academics but through the rise of new and innovative biotechnology companies. I see translational research development as similar to the computer industry during its maturation in the 1980s-1990s: government-sponsored research gave way to an innovative, entrepreneurial spirit. As Associate Dean at Mount Sinai, I am very excited to participate in the emergence of a new design/technology/entrepreneurship PhD and in joining with others to put a greater emphasis on training our young scientists to innovate. We need to help young scientists embrace risk, in science and in their career goals.

How did you become involved with DMM and what made you accept the role of Editor-in-Chief?

Matthew Freeman asked for suggested changes for DMM. I sent him my thoughts – probably a longer list than he expected – and he gave me a chance to defend my vision. DMM has been a pioneer in that the journal focusses on models that impact disease. The next logical step for the journal is to bring in papers that not only look at basic models with implications for disease but also push forward into therapeutics. This requires a broad knowledge that was impossible to find in one person. Although I have the tag of Editor-in-Chief, I will be sharing responsibility for steering DMM with Monica Justice and George Tidmarsh. Monica is a leader in creating basic research models in vertebrates, I provide the invertebrate model experience, and George is a serial entrepreneur and CEO of La Jolla Pharmaceuticals who brings his expertise in translational research in the context of a commercial environment.

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What do you feel is the main benefit of the journal in this field of science and how would you like to contribute in your new role?

DMM has become an important journal for basic researchers who are doing translational science. My guiding vision is simple: I want to work with my partners to create a merged academic and pharmaceutical community. This will include research papers from both worlds, commentaries designed to teach us how to do disease research, and the creation of structures to connect students and postdocs with jobs in biotechnology or pharmaceutics.

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

I like to play guitar and to experiment with computer-generated music. Generally, in my time off I like to hang with my family, who are even more fun when we get the chance to explore New York City together!

If you had to give up science tomorrow and switch career completely, what would you most like to do?

When I was a musician I had to get others to play what was in my head. Now that we can use computers to do that, I might be tempted to take another shot at it.

What is your greatest achievement outside of science?

My wife and I have two daughters – Maya and Jazz – who are smart, ambitious and cool. I'm an old-school feminist (when did feminism go out of style?) and I look forward to watching them walk their own road.

What one thing would people be surprised to learn about you?

Probably the number of different colours my hair was dyed when I entered graduate school.

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