RNA-based therapeutics

Over the past decade, advances in the RNA field have revealed new opportunities for the development of therapeutics, in particular those based on RNA interference (RNAi). Our two interviewees this month discuss their career progression into roles that investigate these opportunities.

Phillip D. Zamore, Ph.D. Co-director, RNA Therapeutics Institute and Gretchen Stone Cook Professor of Biomedical Sciences, University of Massachusetts Medical School, Worcester, Massachusetts, USA. Investigator, Howard Hughes Medical Institute, Chevy Chase, Maryland, USA.

In July 2009, Phillip Zamore became Co-Director of the new RNA Therapeutics Institute at the University of Massachusetts Medical School alongside his colleagues Craig Mello, Melissa Moore and Victor Ambros. "By interweaving basic and applied nucleic acid scientists with clinicians dedicated to finding cures, our goal is to create a new paradigm for organizing molecular research that enables the rapid application of new biological discoveries to solutions for unmet challenges in human health," explains Zamore.

His interest in the field was first sparked during high school, when he enrolled in a Saturday morning course at Columbia University in New York, USA. "One semester was a lecture course on the ribosome," he recalls. "I was in heaven! I knew immediately that I wanted to study molecular machines." So, from the start of his academic career, Zamore had a clear idea of the research path that he wanted to follow. "I had this plan to study biochemistry first and then apply it to animal development. Ultimately, I wandered into the greatest adventure imaginable: RNAi."

His Ph.D. research in biochemistry and molecular biology with Michael Green at Harvard University, USA, and his postdoctoral research with Ruth Lehmann at The Whitehead Institute for Biomedical Research, both in Cambridge, Massachusetts, proved pivotal to this adventure. "Remarkably, many of the key genes in early *Drosophila* development — the genes I had studied or read about during my postdoc — are part of the piRNA [piwi-interacting RNA] pathway. One of my colleagues teases me that I spent years preparing the tools and knowledge needed for the work that I now do in my lab."

Zamore first began working on RNAi in 1999, during the final months of his postdoctoral research. "Tom Tuschl, Phil Sharp, Dave Bartel and I set out to develop an *in vitro* system that would recapitulate RNAi, allowing its biochemical dissection. Later that year, I took up my faculty position at University of Massachusetts Medical School, continuing and expanding our collaborative studies."

Now, as the Gretchen Stone Cook Professor of Biomedical Sciences, and as an investigator of the Howard Hughes Medical Institute, his group of ~20 postdocs, students and staff seek answers to fundamental biological and mechanistic questions about RNA silencing pathways, primarily in flies and in mammals. In addition, the plan with the new RNA Therapeutics Institute is to: " … unite basic, applied and clinical researchers in the development of RNA-based or RNA-targeting drugs or diagnostics."

Throughout his career he has been driven by curiosity. "I love figuring out how things work — whether it is house construction or the innards of a cell. Plus, I'm pretty mad that nature still won't tell me how primary piRNAs are made!" Zamore recommends that researchers should love the subject they study. "If you aren't passionate about your research problem, you won't be able to do your best work."

Antonin de Fougerolles, Ph.D. Vice President of Research, Immunology, Metabolic and Viral Disease, Alnylam Pharmaceuticals, Cambridge, Massachusetts, USA.

Alnylam Pharmaceuticals is developing new therapies based on RNAi technology for a wide range of indications. In his role as a Vice President of Research at the company, Antonin de Fougerolles helps oversee the development of such therapeutics. "I focus on developing RNAi therapeutics in the fields of immunology, virology and metabolic disease. Beyond progression of the therapeutic programmes, a significant amount of my work involves researching ways to address one of the key challenges in the field: delivering siRNA [small interfering RNA] to particular tissues and cell types *in vivo*," he explains.

de Fougerolles' research path began as an undergraduate at McGill University in Montreal, Canada, studying microbiology and immunology. His interest in immunology was consolidated through a Ph.D. at Harvard University in Cambridge, Massachusetts, followed by a 5-year postdoctoral fellowship at the Wellcome Trust's Immunology Unit at the University of Cambridge, UK. "Initially, I focused on basic *in vitro* understanding of molecular mechanisms of leukocyte adhesion, signal transduction and activation," he says.

After his postdoctoral studies, de Fougerolles decided to move into industry with the aim of transitioning his research interests to answer the same *in vitro* questions in more complex *in vivo* preclinical situations. "I found my position in the Department of Experimental Biology at Biogen through an informal network of scientists and collaborators, which I developed during my doctoral and postdoctoral studies," he says.

While at Biogen, de Fougerolles progressed from Scientist to Principal Scientist over 5 years. During this time, the RNAi therapeutics field was just emerging. "The discovery of siRNA and the ability to selectively turn off any mRNA had been demonstrated in cell culture and it was the challenge of applying this technology to the development of drugs that was most appealing," says de Fougerolles, explaining his decision to move to Alnylam Pharmaceuticals in early 2003.

The move to Alnylam Pharmaceuticals also gave de Fougerolles the opportunity to bring together his *in vitro* and *in vivo* expertise to the RNAi field; "to advance products that ultimately will impact patients' lives," he says. "To be able to work on trying to develop a potentially new class of therapeutic represented a rare opportunity and one worth taking."

In his current role, de Fougerolles says it is important to maintain a balance between focused and opportunistic research. "These aren't mutually exclusive, and it is a fine balance between focusing on a few promising research areas to ensure they advance rapidly, while at the same time being open and flexible enough to identify potential new breakthrough opportunities."

Working in RNA biology continually presents de Fougerolles with this challenge. "The recent work on RNAi, microRNA and other non-coding RNA is revolutionizing how we think of the role of RNA in cell biology and physiology. It demonstrates to me the fact that — despite how advanced or well understood we think a field may be — there remains so much more to be discovered."

WEB SITE
Career snapshots: http://www.nature.com/drugdisc/nj/nj_dd_arch.html