

25 Voices of SMA

Adrian R. Krainer, Ph.D.



Who am I?



As a research scientist, I try to understand the nuts and bolts of how genes are expressed, and to devise effective ways to apply this knowledge towards a cure for SMA.

Dr. Krainer is the St. Giles Foundation Professor of Molecular Genetics at Cold Spring Harbor Laboratory, in Long Island, NY. His lab studies the basic mechanisms and regulation of human pre-mRNA splicing, as well as the involvement of this cellular process in genetic diseases and cancer. He is developing mechanism-based methods to correct the genetic defect in SMA, and is a member of FSMA's Scientific Advisory Board.

Why did I become active in SMA?

I first heard about SMA when I was invited to a workshop at NINDS shortly before the seminal Lorson et al paper in PNAS was published in 1999. The work was discussed there, and showed that a single nucleotide change in *SMN2* caused skipping of exon 7; this meant that correcting the splicing defect could be the way to cure this disease. As it happened, the basic research that my lab was already doing on splicing mutations in other genes, such as *BRCA1*, converged remarkably well with these findings. With much encouragement from Alex MacKenzie, Arthur Burghes, and others, I jumped into the SMA field shortly thereafter. I could sense right away that there was something special about the SMA research, clinical, and patient/family community, which really attracted me to this field.

What is my contribution?

The first thing we did was to develop a cell-free system to study how exon 7 is recognized during pre-mRNA splicing. This system has been helpful both to screen and characterize compounds that act directly on the splicing machinery to correct *SMN2* splicing, and to investigate what splicing factors are responsible for the differential recognition of exon 7 in *SMN1* and *SMN2*. We showed that the RNA-binding protein SF2/ASF is a key factor in this process.

We have also put a lot of effort into developing PNA-peptide conjugates and antisense oligonucleotides that can efficiently correct the splicing defect in *SMN2*. This approach is already working remarkably well in mice, and I am very hopeful that before long it will begin to be tested in clinical trials. I am lucky to have had very talented scientists in my group working on SMA, including Luca Cartegni (now at MSKCC), Michelle Hastings (now at Rosalind Franklin University), Yimin Hua, Kentaro Sahashi, and Ying Hsiu Liu, in addition to our close collaborators at Isis Pharmaceuticals and Paratek Pharmaceuticals.

What do I like about FSMA?

It's a long list. I love the annual meetings, especially the warm interactions with the kids and families. I have met fantastic people there, and these interactions really help us to stay motivated and focused when we go back to the lab. FSMA generously funded our collaboration with Paratek. It has truly been an honor to serve on the Scientific Advisory Board.