People & Ideas

David Spector: Coordinating gene expression in space and time

Spector's work focuses on the spatial organization and regulation of gene expression.

PHOTO COURTESY OF COLD SPRING HARBOR LABORATORY

David Spector

Growing up in Washington Heights in New York City, David Spector's interest in science began at a very young age. In the fifth or sixth grade, his class was part of a trial NSF program, called: "Time, Space, and Matter: Investigating the Physical World." Instead of learning by reading materials, the goal of the program was to learn by experience and discussion. As part of this program, the students were handed a blank notebook and asked to write about what they were learning, essentially writing their own "book." His first experience in science came around the same time, when he and his classmate Stanley Feldman built an electronic oscillator and entered the science fair. They won first prize in the Borough of Manhattan Science Fair for fifth and sixth graders and won a whopping prize of $10 each.

Spector has come quite a long way since these early days as a young scientist. He now runs his own lab at Cold Spring Harbor Laboratory (spectorlab.cshl.edu), where he studies the ways in which nuclear organization impacts gene expression. We contacted him to learn more.

Where did you study before starting your own lab?

I received my BS in biology from the City College of New York. There I did a senior research project with Professor Lawrence J. Crockett. He taught me the practical principles of electron microscopy and, hence, "imaging" became a central core of my approach to addressing biological questions. At the same time, Crockett was an amateur playwright and convinced me to play Juan, one of Pope Alexander VI's sons, in a play he wrote starring a full cast of biologists: *Bull of the Borgias*. Amazingly, we were reviewed in *The New York Times*, including a photo (May 9, 1972), by McCandlish Phillips, a theatre critic. I received an MS degree in biology from Herbert H. Lehman College, where I worked with Professor Thomas Jensen studying the ultrastructure of lichens. For my PhD I went on to Rutgers University, where I worked with Professor Richard Triemer on reproduction and chromosome structure of dinoflagellates, continuing the theme of using microscopy to address biological questions. There were lots of all-night time-course experiments, which ended up being highly productive.

After completing my PhD studies, and one morning while shaving, I decided that it would be useful for those in the field who followed me to have a treatise with all of the basic information on dinoflagellates. Hence, I wrote a proposal to Academic Press, which was accepted, and the book I edited and wrote several chapters for, *Dinoflagellates*, was published in 1984. Toward the end of my PhD studies I went up to the Marine Biological Laboratory in Woods Hole, Massachusetts, to present a talk at the Northeast Algal Symposium. There I met Professors Carl Beam and Marion Himes, two geneticists who were working on dinoflagellates at Brooklyn College. They were interested in my work and asked me what I was doing next; since I had no plans I agreed to spend some time in their laboratory.

> "How are functional domains organized, and...functions carried out, in an organelle [with no] membrane bounded compartments?"

Over the next six months I met a wonderful woman, Mona, now my wife and best friend of 35 years. During that same six months I accepted a position as assistant professor in the Department of Pharmacology at Baylor College of Medicine in Houston, Texas, and we were off to a new world. During my time at Baylor, my Department Chair, Dr. Harris Busch, initiated my interest in snRNPs. After spending 4.5 productive years at Baylor College of Medicine, we decided to move back east and I accepted a position at Cold Spring Harbor Laboratory, where I have been for 31 years and am a professor and Director of Research.

What was it that first drew your interest to nuclear organization and the regulation of gene expression?

My interest in this area initially centered around the spatial aspects of gene expression: how are functional domains organized, and how are functions carried out, in an organelle that itself does not contain any membrane bounded compartments? At the time I entered the field the nucleus was thought of as a "black box" in regard to these and other questions. My laboratory initially focused on nuclear speckles, regions enriched in pre-mRNA splicing factors and other proteins involved in gene expression (1). With the discovery by others of GFP and its variants, we were the first to use GFP to study the dynamics of nuclear proteins in living cells; adding a temporal aspect to our studies (2), the culmination of which was the tour de

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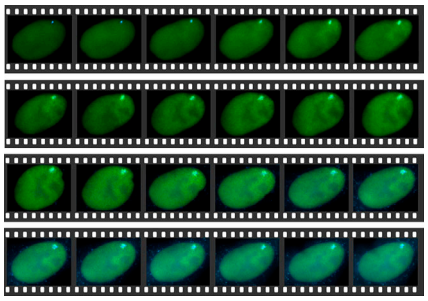

IMAGE ACQUIRED BY SUSAN JANICKI (3)

Visualizing gene expression in living cells. CFP-lac repressor marks the integration site of a 200-copy transgene array. As the locus is transcriptionally induced chromatin decondenses and nascent RNA can be visualized via the recruitment of MS2 coat protein-YFP. The protein product of the transcription units is targeted to cytoplasmic peroxisomes and can be visualized at later time points.

force development of a live-cell imaging system that could inducibly visualize gene expression (DNA, RNA, and protein) in living cells over time (3). In addition, we addressed a series of other questions relating to how nuclear organization is established after mitosis, and how gene bookmarking, monoallelic expression, and allelic pairing can contribute to gene regulation.

What is your lab actively working on?

While continuing to work in these areas, a major focus of the lab today is centered on the role of long noncoding RNAs (lncRNAs) in regulating gene expression and/or nuclear organization (4–6). In this regard, we have decided to focus on breast cancer and differentiation. We have identified a series of lncRNAs that are up-regulated in breast cancer as compared to normal mammary epithelial cells (5). We are pursuing these lncRNAs as new targets that can be manipulated to impact disease progression. In a sense, my research has come full circle as one of these lncRNAs is enriched in nuclear speckles and its knockout or knockdown in animal models of breast cancer results in differentiation of the primary tumor and a significant reduction in metastasis (6). We hope to move these studies into a clinical trial over the next few years.

What kind of approach do you bring to your work?

While we started out as an imaging lab, we are now implementing a wide-range of approaches in our studies including: mouse models, RNA-seq, organoids, human patient samples, histology, and a wide-range of molecular and cell biological approaches.

Was there anything you were unprepared for upon becoming a group leader?

I learned early on to identify interesting questions and keep focused on the problem at hand.

What has been the biggest accomplishment in your career so far?

Looking back over my career there have been two major accomplishments that stand out: (1) Early studies from my laboratory added significantly to developing the concept that nuclear organization and function were intimately linked and that live-cell imaging-based approaches could reveal important insights into understanding nuclear structure and function. (2) A second major accomplishment has been our recent demonstration that knocking out or knocking down *Malat1*, a lncRNA that is enriched in nuclear speckles, results in differentiation of mouse mammary tumors and a significant reduction in metastasis. We hope to move these studies into a clinical trial in the next few years.

> "We must keep pressure on the federal government to increase research funding, ...a critical investment in... our future."

What has been the biggest challenge in your career so far?

The biggest challenge in my career has been the continued uncertainty of research funding. We must keep pressure on the federal government to increase research funding as it is a critical investment in our economy and our future.

Who were the key influences early in your career?

I had several key influences early in my career. The first was Professor Lawrence J. Crockett, whom I mentioned earlier. A second key influence in my career was Professor Bill Brinkley at Baylor College of Medicine. Although I was an assistant professor in the Pharmacology Department, and Bill was a professor in Cell Biology, he was my unofficial mentor and role model during the time I was at Baylor College of Medicine. He was a conduit for experimental and career advice and was always there to talk to and throw ideas around with.

What do you think you would be if you were not a scientist?

It's hard to imagine anything else but science as it combines freedom, creativity, and risk.

Any tips for a successful research career?

Ask important questions and focus, focus, focus.

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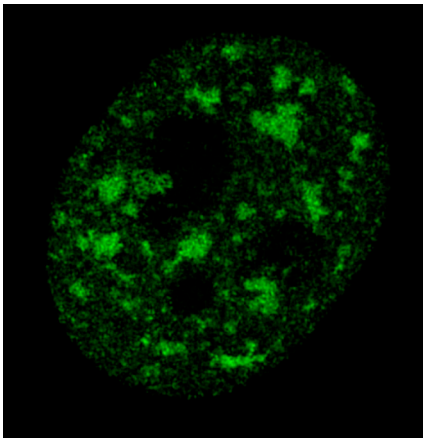

IMAGE ACQUIRED BY ZSOLT LAZAR (1)

Pre-mRNA splicing factors are enriched in a speckled distribution pattern in mammalian cell nuclei. Structured illumination superresolution image of a splicing factor (SC35-EYFP) showing its elaborate organization within nuclear speckles and its diffuse distribution throughout the nucleoplasm.