People & Ideas

Julie Forman-Kay: Dynamic views on protein structure

Forman-Kay provides key structural insights into the biological functions of intrinsically disordered proteins.

Julie Forman-Kay became fascinated with the dynamics of biological systems early on: in grade school, she fell in love with science when she had to observe the metamorphosis of mealworms into adult insects. Her interest in biological dynamics grew stronger and more molecular during her undergraduate studies in chemistry at MIT, where she worked with famed biophysicist Alexander Rich, biochemist Lee Gehrke, biotechnology pioneer Robert Langer, and crystallographer Gregory Petsko. In particular, her time in the Petsko lab, where she was directly supervised by Stephen Burley and also interacted with John Kuriyan (now at Rutgers and UC Berkeley, respectively), set her on the path of combined experimental and computational structural biology.

For her doctoral studies, Forman-Kay set out to study the structure of the disordered fragments of the bacterial protein thioredoxin with Fred Richards at Yale. With sample aggregation plaguing the project, Julie switched to determining the structure of human thioredoxin by NMR near the end of her PhD and continued during her postdoc in the joint lab of Angela Gronenborn and Marius Clore at the NIH. With these critical NMR skills, she set up her lab at The Hospital for Sick Children.

> "I learned that the scientific question should drive the research program, and not the tools used."

In one of her first projects, she conducted a structural study of a folded SH3 domain from the Drk signaling protein. She found that the folded state exchanged with its disordered unfolded state and was able to characterize the fluctuating structure that allowed folding and stability. In essence, she was able to accomplish her PhD thesis goals, an ironic twist of fate that she recalls describing to Fred Richards when visiting Yale years later. Her lab developed several methods applicable to intrinsically disordered proteins to understand the interplay between dynamics, disorder, and function. We contacted her to learn more about her work and career.

What are you currently working on, and what is up next for you?

I have many (too many!) projects ongoing in the lab. Most focus on intrinsically disordered regions (IDRs) of proteins, which, unlike folded domains, do not adopt a stable ordered structure. Instead, their function exploits the large conformational heterogeneity and dynamic sampling of the disordered state (1). We have recently gotten very excited by the phase separation or other large-scale dynamic association of disordered regions in forming cellular structures such as membrane-less organelles, neuronal RNA granules, signaling clusters or puncta, and more.

In addition, we are quite interested in the effects of posttranslational modifications on IDR structure, binding, and phase separation. We are also interested in getting our ENSEMBLE computational approach to describe disordered states "out there" in a more accessible way and with improved algorithms. ENSEMBLE was developed in order to define sets of structures that together represent a disordered state, initially focusing on the Drk SH3 unfolded state and more recently on intrinsically disordered proteins and their dynamic complexes. Structure determination for folded proteins is highly developed, but tools for disordered states are really in their infancy. While we are interested in general concepts and tools, we clearly get excited by the individual systems we study and their connection to health and disease, including the protein mutated in cystic fibrosis, CFTR; the multifunctional protein EWSR1, which is mutated in neurodegenerative diseases and found as an abnormal fusion protein in cancer; interactions of the regulatory complex that controls mRNA translation and is implicated in cancer and autism, 4E-BP2:eIF4E, and of Sic1:Cdc4, a regulatory complex controlling cell cycle that is a model for cancer. We are increasingly interested in neurological function and disease; we are, for instance, starting to study the interactions of the glutamate receptor NMDAR, which has been implicated in stroke and chronic pain.

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Julie Forman-Kay

What kind of approaches do you bring to your work?

We utilize nuclear magnetic resonance, isothermal titration calorimetry, differential scanning calorimetry, fluorescence, mass spectrometry, small-angle X-ray scattering, microscopy, computational tools of all sorts, mammalian cell culture, biochemistry, and more. The "approach" is not tool oriented but conceptual. We are searching for principles of how biology exploits dynamics and disorder for function and how multivalent, dynamic interactions (controlled by posttranslational modifications) can lead to rheostats, switches, and phase separation, with emergent properties.

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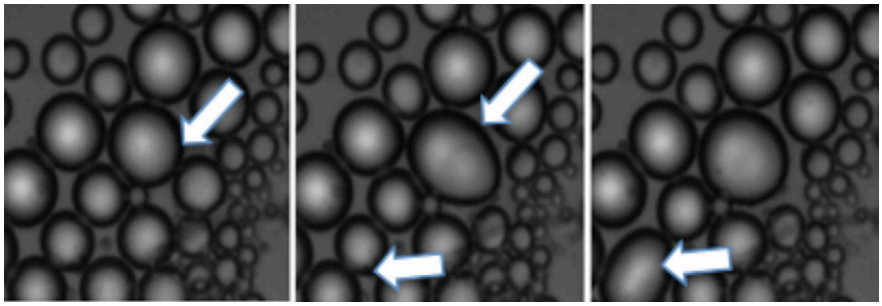

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Phase-separated droplets of an intrinsically disordered arginine- and glycine-rich polypeptide that may play a role in formation of RNA granules, demonstrating liquid behavior of droplet coalescence with panels from the same field separated by two minutes (white arrows).

What did you learn during your PhD and postdoc that helped prepare you for being a group leader? What were you unprepared for?

I learned that the scientific question should drive the research program, and not the tools used. However, new methods can completely open up possibilities for new science. Communication is more than 50% of science. Mentoring is essential. In terms of what I was not prepared for, I was not initially well equipped in dealing with the financial aspects of grant budgeting and some of the fund-raising from foundations and venture capital companies.

> "Always be fully present in every personal interaction you have."

Who were your key influences early in your career?

All my mentors/supervisors, particularly Fred Richards. For Fred, science was about illuminating unsolved questions about fundamental physical and chemical principles underlying biology. While he made critical contributions to the field of protein crystallography, his lab was not a "crystallography" lab. Instead, Fred utilized an array of techniques, including computational simulations, organic synthesis, NMR, hydrogen exchange kinetics probed by radioactive tritium (done in a deeply buried room underneath the chemistry department), and crystallography. This approach to science contrasted with many structural biologists who define themselves by the techniques they use. Fred also strongly emphasized the importance of communication, which he insisted was more then half of good science, and carefully critiqued our lab presentations and graphics to make this point. Fred's lab was a real community, with Johnnie Mouning (the lab manager) and his wife, Thelma (who was in charge of washing glassware), acting almost as parents, giving life advice, and a strong sense of camaraderie within the whole lab, including opportunities for philosophical discussions. I have tried to model my approach to science after his and to create a lab community in many ways as Fred did.

What is the best advice you've received?

There are two that stand out. The first is to always be fully present in every personal interaction you have. The second, don't be concerned about what other people are doing or thinking, but rather just do what seems to be the best thing at any given time.

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

I don't see any individual paper or system I have studied as the "biggest." The impact of the collection of my work in highlighting the critical role of dynamics and disorder in biology and providing tools to help study them is what I consider my biggest accomplishment. This could be stated as essentially being a key part of changing the scientific perspective from a structure–function to a structure/dynamics/disorder–function paradigm.

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

Juggling is the biggest challenge—work and family, administrative demands and research, individual projects with each other…there is never enough time!

What hobbies do you have?

I enjoy playing classical chamber music (violin), reading, and hiking.

What has been your biggest accomplishment outside of the lab?

My two kids: Raphael, age 18, and Shira, who is 12 and a half!

Any tips for a successful research career?

Follow your passion. Don't get trapped in fixed ways of understanding how biology works or set tools for studying it; let yourself be drawn to new ideas and approaches. Collaborate and fill your lab with senior people so that you can always be part of a multi-voiced, experienced conversation about scientific ideas.

1. Forman-Kay, J.D., and T. Mittag. 2013. *Structure*. 21:1492–1499.

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Forman-Kay on a hike in the Alps around Les Diablerets, Switzerland, during the 2016 IDP Gordon Research Conference.