Julie Forman-Kay, PhD

- Hospital for Sick Children Research Institute, Molecular Structure & Function, Senior Scientist
- University of Toronto, Biochemistry, Professor

We study the structure, dynamics, and binding of the cytoplasmic regions of the cystic fibrosis transmembrane conductance regulator (CFTR) and the differences between wild type and delta-F508 mutant CFTR. We want to understand how phosphorylation of disordered elements affects the function and processing of CFTR and how mutant CFTR changes this. We are also interested in how cystic fibrosis (CF) modulator compounds act. A unifying focus is that the disordered regions of CFTR are key regulatory elements and our expertise in understanding disordered regions allows us to provide insight to how CFTR is regulated.

Using nuclear magnetic resonance (NMR), other biophysical and computational approaches, we characterize the structural and binding properties of the cytoplasmic portions of CFTR, including NBD1, NBD2, the regulatory (R) region, and the C-terminal 40 residues. The intrinsically disordered nature of the R region, the regulatory insertion (RI) within NBD1, and the C-terminal 40 residues has enabled our expertise in methods for characterizing disorder to be applied to better understand CFTR structure, dynamics and regulation. We are particularly interested in coupled conformational and binding events and perturbations in these due to phosphorylation, the F508del mutation, and binding of CFTR modulators.

Our findings will potentially lead to improved treatment for CF patients because we are looking at understanding the fundamental defects of the proteins themselves, that is, the differences in the protein energetics, interactions, and structure between the wild type and the mutants. The most effective way to treat the disease would be if we can find a compound that addresses the very fundamental defect at the level of the protein that is mutated. Our insights into the disordered regions of CFTR that are involved in its regulation and how it is different between wild type and delta-F508 are very important for guiding pharmaceutical approaches. Sharing the insights that we have with pharmaceutical companies will help them with rational drug design and mapping a mechanism of action of CF modulators.

My interest in basic and translational research comes from being a physical chemist. I am interested in how biology works in terms of the energetics of biological macromolecules. I was drawn into translational applications because it turns out that our interest in the biophysics of disordered protein regions is hugely relevant to disease processes, because disordered protein regions are one of the primary means of regulating biology. So our interest in the biophysics of disorder leads us into clinically relevant translational applications. It is nice to be able apply biophysics to help people.

My opportunity for real translational applications came when I was collaborating with Philip Thomas of UT Southwestern Medical Center and he got me involved in the United States CF Foundation on an advisory role for the project with a pharmaceutical company that was working on modelling CFTR in order to design drugs. With that project and my connection to the US CF Foundation, I became very involved in translational research. I became involved in CF research when I was recruited to SickKids partly in order to work on structural problems, and with SickKids' major interest in CF, my work has involved studying the structure of domains of CF.

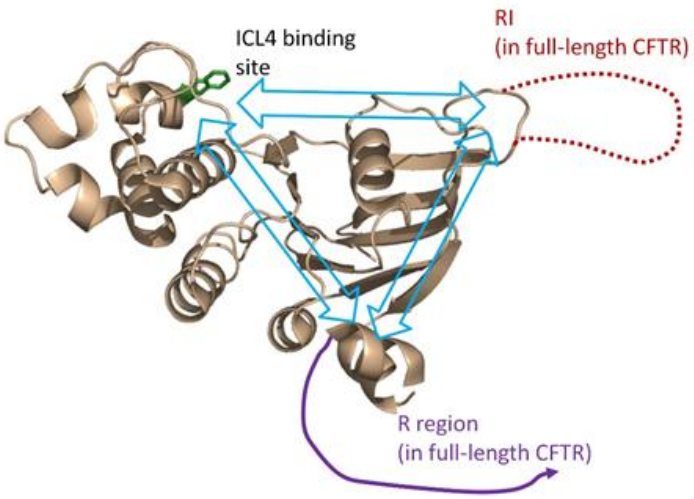
Click here for a complete list of Dr. Julie Forman-Kay's publication at NCBI PubMed.

Trainees:

Andrew Chong (research assistant) – We use NMR, a technique for probing protein structure and motion, to study the effects of CF causing mutations on the inherent motional and functional properties of the first nucleotide-binding domain of CFTR.

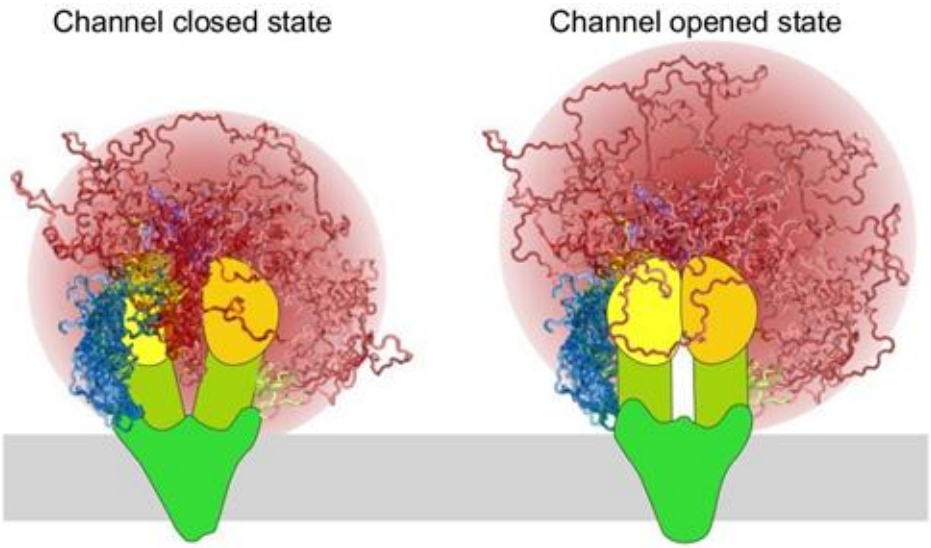
Rhea Hudson (research assistant) – We use NMR approaches to probe the binding of small molecule modulators to the first nucleotide-binding domain of CFTR, where F508del is located, to examine potential conformational changes that may contribute to a mechanism of action for the drug. Such structural level data would not only give information about how a compound functions but also facilitate the design of improved therapeutic compounds.

Jennifer Dawson (research assistant) - Inter-domain interactions are critical for CFTR maturation and gating, especially those between the two nucleotide binding domains (NBDs) and the intracellular loops (ICLs). By the sensitivity of NMR spectroscopy in tandem with correlation statistics analysis, an allosteric network was revealed within CFTR's NBD1 domain, linking the ICL4 binding site to sites located near to where the phosphoregulatory RI and R regions are found in the full-length channel.



Ribbon diagram of CFTR NBD1with blue arrows schematically representing allosteric coupling between three regulatory sites, the ICL4 binding site that links NBD1 to the channel pore, the C-terminus of NBD1 that is connected to the R region and the site of the regulatory insertion (RI). Both the R region and RI are phosphoregulatory elements of CFTR. NMR data point to coupling between these different regulatory sites.

Zoltan Bozoky (post-doctoral fellow) - The intrinsically disordered regulatory region of CFTR controls the channel processing and gating by interacting with intra- and intermolecular partners in a phosphorylated dependent manner. One goal is to understand and characterize the structural and functional heterogeneity of this unique region, including the development of computational models for the R region within the context of full-length CFTR in different states.



Schematic models of (left) non-phosphorylated/closed channel and (right) PKA-phosphorylated/open channel states of CFTR showing the N-terminal segment (blue), membrane spanning domains (dark green), the intracellular domains (yellow-green), NBD1 (yellow), NBD2 (gold), R region (red) and the C-terminal segment (purple). Disordered elements (N-terminus, R region and C-terminus) are shown as a superposition of multiple possible conformations. The gap between the ICDs (white, in right figure) schematically illustrates the open channel pore, the membrane is represented as a gray bar and the R region sampled space is colored as a gradient (red of various intensities).

Mickael Krzeminski (post-doctoral fellow) – One project aims at characterizing the R-region of the human CFTR protein using experimental data (NMR, X-ray) coupled with computational approaches (ENSEMBLE). The latest version of ENSEMBLE that we developed, which is widely used today among structural biologists interested in IDPs, will allow more accurate results and better convergence. We plan to integrate into ENSEMBLE more data types, e.g. secondary structure propensity and single molecule FRET.

Robert Vernon (post-doctoral fellow) – I study how CFTR's intrinsically disordered regions interact with each other and with CFTR's nucleotide binding domains, using NMR spectroscopy and computational modeling approaches to explore the roles these interactions play during protein folding as well as in regulating CFTR activity.

SickKids Hospital > Julie Forman-Kay Profile

SickKids Hospital > Research > Researchers in profile > Interview with Julie Forman-Kay

University of Toronto > Department of Biochemistry > Julie Forman-Kay Profile

University of Toronto > Julie Forman-Kay Lab

Cystic Fibrosis Foundation > CF Research Consortia