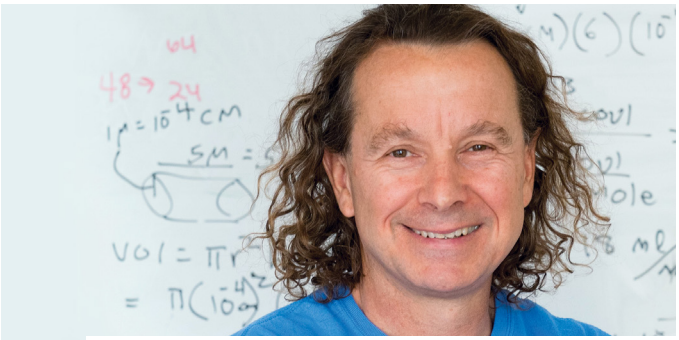

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Biological molecules are the elementary building blocks comprising organelles, cells, and life forms. We seek to understand how these building blocks assemble into higher-order, mesoscale patterns from which cellular structure and function emerge. To this aim we exploit the inherent 2-dimensionality of membranes to analyze protein interactions using various biophysical methods including electron and fluorescence microscopy.

For several decades the MacKinnon lab focused on the structures and mechanisms of membrane proteins called ion channels. These proteins underlie the electrical system of life by converting chemical and mechanical stimuli into electrical signals and propagating those signals in the form of electrical impulses. The lab determined the first structures of a selective ion channel, the K^+ channel, to understand how it discriminates between K^+ and other ions, especially the closely related alkali metal ion Na^+. Following this work on ion conduction and selectivity, the MacKinnon lab sought to understand how ion channels gate their pores so that their activity can be regulated by specific stimuli. They determined the first structures of voltage-dependent ion channels, which underlie the propagation of action potentials, showing how the movement of charged amino acids within the membrane electric field is coupled to opening the pore. They also showed how the binding of ligands, including $Ca2^+$, PIP2, and G proteins, regulate gating through allosteric conformational changes. Most recently, through atomic structures of Piezo ion channels and quantitative analysis of membrane vesicle shapes, they put forth the membrane dome model to explain how these channels sense mechanical force.

Until recently, work in the MacKinnon lab was best described as trying to understand how individual proteins function as 'molecular machines' to accomplish their required tasks. Presently, work in the MacKinnon lab is directed at understanding how different molecules interact with each other to fulfill their biological functions. Such interactions are important for the regulatory control exhibited when G protein coupled receptors (GPCRs) are stimulated, for example. Indeed, all of cell biology depends on the interactions between proteins, mostly non-covalent, to build up every macroscopic component of a cell. To understand how biomolecules assemble to form 'mesoscale' structures we remain focused on the cell membrane to exploit its approximate 2-dimensionality, which makes it easier to quantify interactions. The methods we use include electron microscopy and fluorescence microscopy for imaging, and mass spectrometry, NMR and other biophysical methods for compositional analysis.

Exemplar current projects include: 1) When you have a signal pathway traditionally described as protein1→ protein2 → protein3, with arrows to be read as 'communicate with', what do the arrows physically mean? We have recently discovered that weak, yet specific protein-protein interactions produce clusters that we call higher-order transient structures (HOTS). These bring the 'right' proteins in transient proximity, thus connecting the proteins on average, i.e., statistically. We call this new concept dynamic connectivity and examine its applicability to numerous GPCR pathways. 2) We have found that cell membranes spontaneously segregate into protein rich islands with intervening protein poor regions, which we can isolate and examine compositionally. These appear to support unique cellular functions. We seek to understand how and why cell membranes organize this way. 3) Cellular structures emerge through the spontaneous self-assembly of proteins, lipids and other molecules. We posit the existence of non-covalent chemical rules that permit this to occur and seek to discover these rules. 4) Using cryo-EM tomography we are determining the structure of the node of Ranvier, which is the specialized structure in myelinated nerve fibers that permits rapid nerve conduction.

EDUCATION

B.A. in biochemistry, 1978
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Tufts University School of Medicine

MEDICAL TRAINING

Residency in internal medicine, 1982–1985
Beth Israel Hospital, Harvard Medical School

POSTDOC

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POSITIONS

Assistant Professor, 1989–1992
Associate Professor, 1992–1995
Professor, 1995–1996
Harvard Medical School

Professor, 1996–
The Rockefeller University

Investigator, 1997–
Howard Hughes Medical Institute

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AWARDS

Albert Lasker Basic Medical Research Award, 1999

Lewis S. Rosenstiel Award, 2000

Canada Gairdner International Award, 2001

Perl-UNC Neuroscience Prize, 2001

Nobel Prize in Chemistry, 2003

Louisa Gross Horwitz Prize, 2003

HONORARY SOCIETIES

National Academy of Sciences

American Philosophical Society

SELECTED PUBLICATIONS

Mandala, V. et al. Spatial deconstruction of the plasma membrane. *bioRxiv* DOI: 10.1101/2025.11.14.688519 (2025).

Mandala, V. et al. Molecular contacts in self-assembling clusters of membrane proteins. *Proc. Natl. Acad. Sci. U.S.A.* 122, e2507112122 (2025).

Mandala, V. and MacKinnon, R. Electric field–induced pore constriction in the human Kv2.1 channel. *Proc. Natl. Acad. Sci. U.S.A.* 122, e2426744122 (2025).

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