Interface Mimicry-Based Prediction of Host-Microbe Interactions

Emine Guven-Maiorov, Asma Hakouz, Ozlem Keskin, Attila Gursoy, Chung-Jung Tsai & Ruth Nussinov

Cancer and Inflammation Program, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, National Cancer Institute at Frederick, Frederick, MD 21702, U.S.A

Signaling pathways shape and transmit the cell's reaction to its changing environment; however, microbes can circumvent this response by manipulating host signaling. To subvert host defense, they beat it at its own game: they hijack host pathways by mimicking the binding surfaces of host-encoded proteins. For this, it is not necessary to achieve global protein homology; imitating merely the interaction surface is enough. Different protein folds often interact via similar protein-protein interface architectures. This similarity in binding surfaces permits the pathogenic protein to compete with a host target protein. Thus, rather than binding a host-encoded partner, the host protein hub binds the microbe surrogate. The outcome can be dire: rewiring or repurposing the host pathways, shifting the cell signaling landscape and consequently the immune response. They can cause persistent infections as well as cancer by modulating key signaling pathways. Mapping the rewired host-pathogen 'superorganism' interaction network is critical for in-depth understanding of pathogenic mechanisms and developing efficient therapeutics. The talk will discuss the role of molecular mimicry in host evasion and describe a method, HMI-PRED, that we have developed to decipher it. Given the structure of the microbial protein it predicts structural models of potential host-microbe interaction complexes, the list of mimicked/disrupted host endogenous, tissue expression of the microbe-targeted host proteins, and the **structural superorganism network**.

Ruth Nussinov – Short bio

Ruth Nussinov is a computational structural biologist at the NCI. Her Ph D thesis proposed the dynamic programming algorithm for the prediction of RNA secondary structure, which is still the primary method toward this aim. She was among the pioneers of DNA sequence analysis, proposed the fundamental concept of Conformational Selection and Population shift as an alternative to the textbook 'Induced-Fit' model in molecular recognition. Her studies unveiled the key role of allostery under normal conditions and in disease and the principles of allosteric drug discovery. She also proposed that proteins whose sequence and global structures differ may still share similar interface architectural motifs. This concept serves as a basis for the prediction of protein interactions. She was among the first to model amyloid conformations. During the last few years she has been focusing on signaling processes in cancer, mechanisms of activation of oncogenic proteins and implications to drug discovery.

Dr. Nussinov received her Ph.D. in 1977 from Rutgers University and did post-doctoral work in the Structural Chemistry Department of the Weizmann Institute. Subsequently she was at the Chemistry Department at Berkeley, the Biochemistry Department at Harvard, and a visiting scientist at the NIH. In 1984 she joined the Medical School at Tel Aviv University. In 1985, she

accepted a concurrent position at the National Cancer Institute of the NIH, Frederick national Laboratory for Cancer Research, where she is a Senior Principal Scientist and Principle Investigator heading the Computational Structural Biology Section at the NCI. She has authored over 600 scientific papers. She served as the Editor-in-Chief of PLOS Computational Biology and Associate Editor and the Editorial Boards of several journals. She is a frequent speaker in Domestic and International meetings, symposia and academic institutions, won several awards and is an elected Fellow of the Biophysical Society and the International Society for Computational Biology. She is a Highly Cited Researcher (ranking among the top 3000 researchers or 1% across all fields according to Thomson Reuters Essential Science Indicators, http://highlycited.com/ December 2015 and 2019), earning them the mark of exceptional impact. She also won an award from the AACR in 2017 for her paper on The Key Role of Calmodulin in KRAS-Driven Adenocarcinomas. Her National Cancer Institute website gives further details. https://ccr.cancer.gov/ruth-nussinov.