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A ubiquitous family of cell-surface receptors called G protein coupled receptors act as transducers for myriad processes, ranging from color vision to hormone signaling to synaptic transmission. These receptors are also the targets for approximately one-third of therapeutic drugs. The Sakmar laboratory examines the molecular mechanisms by which G protein coupled receptors work and develops new technologies to advance drug discovery targeting cancer, inflammation, and autoimmune disorders.

The primary research focus of the Sakmar laboratory is to study the biology and chemistry of heptahelical G protein-coupled receptors (GPCRs). The mechanism of transmembrane signaling by heptahelical receptors is an area of intense scientific interest that has tremendous biological and pharmaceutical relevance.

The laboratory has pioneered novel methods, including genetic code expansion to introduce unnatural amino acids into expressed receptors, as a tool for GPCR-targeted drug discovery. The researchers recently adopted a variety of ancillary experimental approaches, including targeted photocrosslinking to map ligand and antibody binding sites; bioorthogonal labeling reactions to introduce site-specific fluorophores; and monoclonal antibody epitopes to facilitate single molecule imaging studies. These strategies can be combined with traditional approaches to study GPCRs, channels, and other difficult-to-express membrane proteins.

Sakmar's work has focused primarily on family A GPCRs, also known as the rhodopsin family, as a model system for biophysical studies, and chemokine receptors for studies of ligand recognition and proteomics. Chemokine receptors control cell migration and also act as coreceptors for HIV-1 cellular entry. Other receptors and aspects of G protein-mediated signaling are also under investigation. In particular, the lab is studying downstream cytoplasmic components of G protein signaling pathways, with a particular interest in defining protein-protein interactions that modulate crosstalk between signaling pathways. In addition, the lab has studied how mutations in genes encoding GPCRs result in expressed receptors with high levels of basal activity. One such gene, CYSLTR2, causes a rare ocular cancer called uveal melanoma, and is the first known example of a GPCR "driver" oncogene.

Proteomics approaches to elucidate the roles of accessory regulatory proteins that interact with GPCRs are also under study. This work uses novel suspension bead array assays facilitated to engineering GPCR expression libraries and curated antibodies from the Human Protein Atlas.

A new area of research in the Sakmar lab focuses on human protein folding disorders and amyloidosis syndromes. The lab has discovered novel chaperone-like amyloid-binding proteins that can be engineered to stabilize transient amyloid intermediates and create unique panels of monoclonal antibodies with diagnostic or therapeutic potential.

EDUCATION

A.B. in chemistry, 1978
University of Chicago

M.D., 1982
University of Chicago Pritzker School of Medicine

MEDICAL TRAINING

Internship in medicine, 1982–1983
Residency in medicine, 1983–1985
Massachusetts General Hospital

POSTDOC

Massachusetts Institute of Technology, 1985–1990

POSITIONS

Assistant Professor, 1990–1994
Associate Professor, 1994–1998
Associate Dean for Graduate Studies, Tri-Institutional M.D.-Ph.D. Program, 1997–2002
Professor, 1998–
Acting President, 2002–2003
Director, Pels Family Center for Chemistry, Biochemistry and Structural Biology, 2002–2005
The Rockefeller University

Physician, 1995–2000
Senior Physician, 2000–
The Rockefeller University Hospital

Assistant Investigator, 1991–1994
Associate Investigator, 1994–2004
Howard Hughes Medical Institute

SELECTED PUBLICATIONS

Ham, H. et al. Germline mutations in G protein identify signaling cross-talk in T cells. *Science* 385, eadd8947 (2024).

Huber, T. et al. The role of CYSLTR1/2 GPCR-signaling pathways in regulating melanocyte proliferation and senescence. *Sci Signal* 17, eadp3967 (2024).

Kotliar, I.B. et al. Multiplexed mapping of the interactome of GPCRs with receptor activity-modifying proteins. *Sci. Adv.* 10, eado9959 (2024).

Mattheisen, J. M. et al. Bioorthogonal tethering enhances drug fragment affinity for G protein-coupled receptors in live cells. *J. Am. Chem. Soc.* 145, 11173–11184 (2023).

Dahl, L. et al. Multiplexed selectivity screening of anti-GPCR antibodies. *Sci. Adv.* 9, eadf9297 (2023).