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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.

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.

A new area of research in the Sakmar lab focuses on human protein folding disorders and amyloid syndromes. Members of the lab have discovered novel chaperone-like amyloid-binding proteins that can be used to stabilize transient 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

Kowalski-Jahn, M. et al. Frizzled BRET sensors based on bioorthogonal labeling of unnatural amino acids reveal WNT-induced dynamics of the cysteine-rich domain. *Sci Adv* 7, eabj7917 (2021).

Lorenzen, E. et al. Multiplexed analysis of the secretin-like GPCR-RAMP interactome. *Sci Adv* 5, eaaw2778 (2019).

Barbash, S. et al. GPCRs globally coevolved with receptor activity-modifying proteins, RAMPs. *Proc. Natl. Acad. Sci. U.S.A.* 114, 12015–12020 (2017).

Cao, Z. et al. Targeting of the pulmonary capillary vascular niche promotes lung alveolar repair and ameliorates fibrosis. *Nat. Med.* 22, 154–162 (2016).

Moore, A.R. et al. Recurrent activating mutations of G-protein-coupled receptor *CYSLTR2* in uveal melanoma. *Nat. Genet.* 48, 675–680 (2016).