ELSEVIER

Model systems
Mimics and probes of biological systems
Editorial overview

Blake R Peterson and Milan Mrksich

Current Opinion in Chemical Biology 2007, **11**:579–580

1367-5931/$ – see front matter

DOI 10.1016/j.cbpa.2007.10.010

Blake R Peterson

Department of Chemistry, The Pennsylvania State University, 104 Chemistry Building, University Park, PA 16802, United States
e-mail: brpeters@chem.psu.edu
URL: http://chemistry.uchicago.edu/fac/mrksich.shtml

Blake Peterson received his BS degree in chemistry in 1990 from the University of Nevada, Reno. He pursued graduate studies in chemistry with Professor François Diederich at both UCLA (1990–1992) and the ETH-Zürich (1992–1994). Following completion of his UCLA PhD in 1994, he joined the laboratory of Professor Gregory Verdine in the Department of Chemistry and Chemical Biology at Harvard University as a Damon Runyon — Walter Winchell Cancer Research Foundation Postdoctoral Fellow. He joined the faculty in the Department of Chemistry at Penn State University as an assistant professor in 1998 and was promoted to associate professor in 2004. In 2008, he will assume the position of professor in the Department of Medicinal Chemistry at the University of Kansas. His laboratory focuses on the synthesis of small molecules that control and probe cellular biology.

Milan Mrksich

Department of Chemistry, University of Chicago and Howard Hughes Medical Institute, 929 East 57th Street, Chicago, IL 60637, United States
e-mail: mmrksich@uchicago.edu

Milan Mrksich received his BS degree in chemistry in 1989 from the University of Illinois and then pursued graduate studies with Professor Peter Dervan at Caltech. He was an American Cancer Society Postdoctoral Fellow in the laboratory of Professor George Whitesides at Harvard University before his appointment as an assistant professor of chemistry at the University of Chicago in 1996. He is currently professor and in 2005 was appointed an Investigator in the Howard Hughes Medical Institute. His laboratory integrates chemistry, materials science, and biology to prepare models of the extracellular matrix for studies of cell adhesion and to prepare biochip arrays for the high-throughput characterization of biochemical activities.

Biology is complicated. Studies of biological systems at all levels — from the function and regulation of individual proteins, to the networks of macromolecules that coordinate cellular activities, and the assembly and maintenance of multicellular organisms — reveal intrinsic complexities that necessitate the use of model systems. Oftentimes, experiments are performed with samples — for example, cell lysates — that contain a multitude of molecules that are not relevant to the activity of interest, and that contain others that are essential but still not characterized. Model approaches that can reconstitute the relevant activity from defined reagents serve an essential role in isolating the problem and in turn enabling subsequent molecular studies. In other examples, the list of parts may be defined, but the rules by which these parts interact remain elusive. This challenge is particularly evident in the spatial organization and regulation of molecules in a cell where colocalization of proteins can be essential to enabling or inhibiting biochemical activities. Again, model systems contribute to defining possible mechanisms and in focusing further studies.

This issue of *Current Opinion in Chemical Biology* emphasizes chemical approaches in the design and application of model systems. A hallmark of these approaches is the reliance on molecular design and synthesis, including small molecules that regulate or visualize protein function and chemical reactivity, biomolecules having non-natural functionality, and molecules used in the assembly of supramolecular structures that mimic cell membranes and other higher order structures. These reagents and structures provide unique tools that are important in framing and studying biological processes. Chemists also bring a sophisticated understanding of molecules — including structures, dynamics, kinetics and thermodynamics of interactions, and reactions — that are fundamental to understanding the roles of these entities at all scales in biological systems.

We have invited six leaders to share their thoughts on the challenges, opportunities, and recent progress in developing biological model systems. These systems span the range from those that address structure in proteins and nucleic acids, the properties and activities associated with membranes, and the study and engineering of complex activities in cells and model organisms.

In the realm of supramolecular assembles, Steven Boxer and Yee-Hung Chan describe recent advances in model membrane systems including vesicles, membranes immobilized on solid supports, and computational simulations of these structures. Because natural membranes differ substantially in composition, even within a single eukaryotic cell, model membranes that correctly reconstitute features of natural membranes are essential for

defining the roles of individual components, their organization, and dynamics. Model systems comprising purified lipid components and more complex structures derived from intact cellular membranes represent key tools for understanding diverse cellular processes at the molecular level. These studies of cellular membranes represent a challenging frontier in chemical biology, but this area is crucially important as signal transduction, endocytosis, trafficking of biomolecules, and many other biological processes depend on the ability of membranes to define distinct areas and control transport within, between, and across lipid bilayers.

Eric Kool examines methods for understanding base pairing using modified nucleobases that differ from natural bases in polarity, size, shape, and functional groups. Model nucleosides and nucleotides have the potential to unlock mechanisms controlling the propagation, origin, and repair of biological systems. These compounds may also facilitate the identification of therapeutics that affect replication, transcription, translation, and other processes, and yield improved tools for genetic analysis. Additionally, the development of efficient non-natural base pairs may eventually lead to artificial biological systems that evolve *in vitro*.

Protein folding remains a popular and important problem for experimentalists and theorists. Our understanding of the mechanisms that operate when a polypeptide folds into a unique tertiary structure has been informed by a range of model systems and now benefits from algorithms that can predict, from primary sequence alone, aspects of secondary and tertiary structures. In this article, Todd Yeates and colleagues introduce proteins that are folded into knotted and other topologically complex structures. The identification of proteins having knotted structures, even when high-resolution structures are available, is challenging and model studies are needed to understand the folding pathways. This article describes results from recent studies showing that knotting confers stability and resistance to proteolysis and suggests strategies for engineering future model systems that can better delineate the functional consequences of this fascinating class of structures.

Biological systems have also become targets for engineering, with a growing interest in manipulating organisms to perform new biological functions. In their contribution, Rustem Ismagilov and Michel Maharbiz extend this concept to the engineering of organisms for the fabrication of nonbiological structures, or biological structures that carry out nonbiological functions. The authors show that rapid advances in microfluidics and microfabrication now provide unprecedented opportunities to spatially and temporally control the chemical environment around cells. These devices allow cells and tissue to be cultured in the nonuniform environments that are intrinsic to *in vivo* studies and therefore provide model systems for understanding the factors that direct cellular differentiation and pattern formation in organogenesis. This review identifies several model organisms and biological activities that provide exciting starting points for building synthetic biotic systems by manipulating the biological machinery that drives development in multicellular organisms.

The regulation of gene expression underlies essentially all aspects of cellular activities and operates at many levels. The finding five years ago that noncoding RNAs can bind small molecule metabolites and suppress the transcription or translation of their associated gene products added a new dimension to the understanding of gene regulation, and also suggests a novel strategy for engineering bacteria with new functions. In a contribution to this issue, Justin Gallivan reviews the early progress in understanding and applying 'riboswitches' that regulate gene expression. It is interesting that while the discovery of riboswitches was a surprise, an understanding of how the RNA molecules could be regulated by small molecules was revealed through earlier studies that used model systems to evolve RNA aptamers that had affinity for small molecules. The article describes an early example of bacteria engineered with a riboswitch that binds theophylline and then activates a key gene in the chemotaxis pathway, allowing the cells to navigate a path of the small molecule without interference from the structurally related caffeine molecule. This example suggests exciting possibilities for engineering bacteria with a range of new functions.

Christopher Chang and Evan Miller discuss advances in fluorescent probes that enable sensing of nitric oxide and hydrogen peroxide, reactive nitrogen and oxygen species that promote oxidative post-translational modifications involved in cellular signal transduction. Nitric oxide is a second messenger of substantial interest thought to be involved in a variety of physiological processes from vasodilation to neurotransmission. Hydrogen peroxide is a hallmark of oxidative stress, a defense agent that is used to inactivate pathogens, and an intracellular oxidizing agent that reversibly oxidizes amino acids to affect cellular processes. Key challenges in this area include the development of selective and sensitive cell-permeant sensors that respond to specific reactive species.

Chemistry has had a long history in developing and applying models to gain insight into biological questions. As evidenced by the articles in this issue, the model systems have grown in complexity and in relevance as the molecular details that underpin biological processes have been elucidated. The interplay between model systems and the biological systems, or between bottom-up and top-down approaches, to complex problems remains a central theme in chemical biology and provides many opportunities for researchers in this field to make important contributions to the biological sciences.