ACCOUNTS
of chemical research

GUEST EDITORIAL

Transport Across Membranes

Membranes are a fact of life. More than just passive barriers separating cells from their environment, they are the dynamic means to control and energize reactions, to process inputs and exports, and ultimately to signal, sense, and respond to stimuli. As a molecular environment, the biological membrane with its lipid core, its integral and peripheral proteins, and its carbohydrate scaffolding is deceptively simple in overall plan but chaotically complex in its detailed organization and dynamics. That chemists are inspired by membranes and transport across the membrane barrier is hardly surprising.

The 25 Accounts in this issue are united in identifying natural membrane components, processes, and structures both as an intellectual starting point and as a target to emulate. From that common inspirational seed, directions diverge, take on a life of their own, and finally reveal as high a level of complexity as the inter-related phenomena of the membrane processes that inspired them. It could not be otherwise; natural membranes are mixtures, and the functions they exhibit are the consequence of complex chemical systems rather than of the individual molecular components of the mixture. So too are the functions of the membrane systems discussed in this issue.

The functional characteristics of membrane transport provide another unifying theme of this issue. The membranes and transporters of the cell are only there because they are useful. The majority of the Accounts of this issue are thus based on the abstraction of the general principles evident or suspected in Nature as they apply to practical goals. The goals vary widely from the subversion of natural membranes for therapeutic ends to industrial separations and technologies entirely divorced from their inspirational roots in biology. A casual browsing of the conspectus graphics will show how many of the contributions demonstrate the interplay of biological starting points and applied end-points.

The protein channels of Nature inspire by their exquisite interplay of structure and function. The Account by Tarek and Delemotte explores the origins of the voltage response of the voltage-gated potassium channel, amply revealing both the structural control and the consequences of the breakdown of that control. In counterpoint, Heimberg and Mosgaard sound a cautionary note that ion conductance via solely lipid channels is electrically similar to features that are usually assigned to protein behaviors, a theme that appears in other papers involving synthetic channels. Channel engineering, the modification of naturally derived peptide and protein channels, is a highly productive strategy to impart additional functions and controls. Futaki and coauthors describe their modifications to the peptide channel alamethicin to influence channel conductance and duration via control of oligomerization and to impart gating control through additional extramembrane segments. Yang and Mayer functionalize the peptide channels of gramicidin to allow them to report on the state of biochemical processes thereby creating sensitive single-molecule probes of potential utility in chemical biology. On a larger scale Feringa, Kocer, and coauthors discuss the modifications to protein channels that render them light sensitive, eventually leading to light-controlled activity of zebrafish. The Account by Koert and Reiß nicely compares the channel engineering strategy to a strategy of de novo design of ion channels through their work on fully synthetic oligo-THF channels, through modifications within the gramicidin channel to manipulations inside the outer-membrane pore protein.

Synthetic ion channels are explored by many authors in this issue. The central challenge is to organize a transmembrane pore using synthetically accessible structures, an approach that allows the creativity of chemists to flower. Voyer and coauthors illustrate the potential of amphiphilic peptide helices as a scaffold to organize a channel of crown ethers. Gokel and Nedin reflect the diversity of structures possible, from membrane-spanning channels based on crown ethers to amphiphilic heptapeptides to metal–organic capsules to hydrogen-bonded isophthalamide channels, all of which show significant channel activity. A similarly diverse set of synthetic channels is discussed by Tecilla and coauthors with structures ranging from hydroxy

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steroid dimers and calixarene clusters to sugar amphiphiles to metalloporphyrin assemblies. Zhao and coauthors highlight the creation of channels for large migrating guests through the use of oligocholate foldamers.

Several authors highlight the potential of self-assembly processes to create transmembrane channels. Granja, Ghadiri, and coauthors describe their work on self-assembling peptide nanotubes built on the stacking of the macrocycles driven by hydrogen bonding in which internal, external, and capping groups influence the assembly and transport processes. The role of macrodipoles in such stacks is discussed in the contribution of Matile and co-workers. Toroidal pores can also be elaborated from highly curved segments as discussed by Lee and coauthors, involving stacking both in the through-membrane direction and around the pore circumference. Barboiu and Gilles describe urea-based channels in the solid state and incorporated into membranes where the active structures are assembled via hydrogen bonding along the pore axis and around the pore periphery. Nonspecific aggregation and self-assembly is the focus of the channels discussed by Fyles, where the structures are assembled in response to the phase preferences of the lipid-transporter mixture.

Natural transport phenomena extend beyond single channels in isolated membranes and a pair of Accounts in this issue discuss approaches that mimic more complex biochemical systems, particularly where a pair of apposed membranes interacts. As formulated by Webb, this is a problem of adhesion, and he shows how adhesion of magnetic particles to pores can result in magnetic switching of channel activity. Ma and Bong focus directly on the approach and mixing of two vesicle membranes resulting in fusion of the lipids and mixing of the contents, ideally without escape to the external environment.

Carrier-mediated transport offers an alternative mechanism for the development of specifically targeted and selective transporters. Valkenier and Davis describe the evolution of neutral chloride specific carriers, effectively the anionic equivalent of the cation carrier valinomycin. Carriers offer significant potential for direct therapeutic applications. Gale and Quesada describe screening of anion receptors against cancer cell lines and the interplay of supramolecular recognition and biological activity. Wender and coauthors provide an overview of the evolution of oligoguanidinium carriers optimized to applications in imaging, diagnostics, and therapies. Although mechanistically distinct, an equivalent evolution of structure and function of amphipathic peptides toward amphiphilic foldamers as antimicrobial agents is outlined in the Account by Tew and coauthors.

As noted above, many of the Accounts in this issue have a strong technological focus. Guan and co-workers examine the potential of modified hemolysin pores as stochastic sensors, a technology holding promise for the simultaneous detection and quantification of single-molecule analytes. Do such nanopore sensors require proteins? The Account of Jiang and coauthors explores this question using 30-nm conical pores created by nanomachining to demonstrate that many macroscopic properties of voltage-responsive membranes can be reproduced by such structures. Regen and coauthors explore an alternative approach to shifting from the molecular scale to technologically relevant materials through the assembly of porous monolayers into layered membranes with unique gas permeability characteristics. Technological applications could utilize interactions apparently ignored in Nature such as those explored in the Account of Matile and coauthors, which illustrates the use of anion$-\pi$ and halogen-bonding interactions to create highly efficient transporter systems remote from any biological roots.

Precisely 40 years after the first synthetic ion channel was reported by the late Iwao Tabushi in *Tetrahedron Letters*, this is the first time that this exceptionally demanding field is brought together at this level. The result is a spectacular array of inspired contributions from most of today's leaders, from the pioneers to the rising stars. We thank the board of editors for their initiative, all authors for their substantial efforts, and you for reading. We certainly hope you will enjoy!

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

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Guest Editors