proaches, including AONs, are being used to target both mutated and wild-type *DNM2* RNA (*14*). A reduction of total *DNM2* expression in a mouse model improved outcome, providing proof of principle that reduced *DNM2* expression could be therapeutic in CNM. A phase 1 open-label study targeting *DNM2* with a constrained ethyl gapmer in CNM patients has recently started.

Biallelic silencing is also being pursued in SOD1-related ALS. In this condition, dominant missense variants of *SOD1* cause toxic effects in motor neurons by increasing oxidative stress. A phase 1 RCT of an AON targeting *SOD1* through intrathecal administration was well tolerated (*15*), and a second-generation AON, BIIB067, is entering a phase 3 RCT for SOD1-ALS.

RNA therapies have made impressive progress with the approval of several drugs and further products in the pipeline. Some clinical failures highlight the need to develop alternative chemistries, conjugates, or delivery systems to improve targeted delivery to muscle. The clinical efficacy of next-generation compounds will be enhanced by better understanding of their uptake and intracellular kinetics. For conditions affecting motor neurons, intrathecal delivery efficiently reaches the brain, although chronic administration of these therapies through this route carries a burden for patients; this could be avoided in the future by AONs that cross the BBB. In AON-mediated silencing approaches, biallelic strategies also raise questions about possible haploinsufficiency-related effects and consequent safety profiles. Studies of these next-generation compounds will clarify the extent of clinical benefit and phenotype reversion in these severe conditions. ■

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MEMBRANES

Why polyamide reverse-osmosis membranes work so well

Inhomogeneities in membrane thickness and density promote water transport

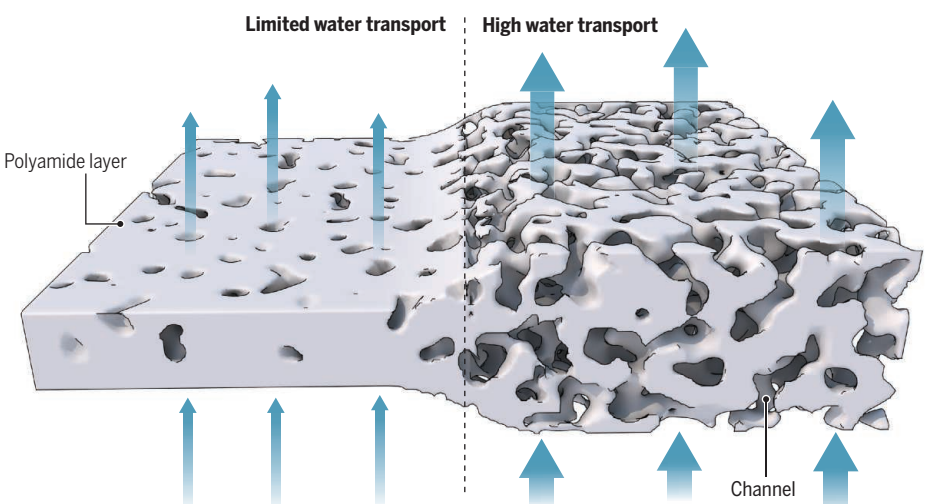
By **Geoffrey M. Geise**

Desalination technology leaped forward with the development of interfacially polymerized reverse osmosis (RO) membranes patented by Cadotte in 1981 (*1*). A huge performance improvement came largely from a selective layer with a self-limiting thickness on the order of 100 nm formed through interfacial polymerization at an oil-water interface on a microporous support (*2*). Continued membrane property improvements realized during the past four decades have resulted mainly from processing or manufacturing modifications that are often proprietary, rather than by modifying the core chemistry or membrane preparation process (*3, 4*). The thin, inhomogeneous selective layer has frustrated efforts to satisfactorily characterize polyamide membrane structure and transport properties for decades (*5*–*7*). On page 72 of this issue, Culp *et al.* (*8*) leverage advances in microscopy and modeling to provide critical insights into structure–property relationships for current state-of-the-art RO membranes that could be used to rationally improve their performance.

Interfacially polymerized RO membranes derive their separation characteristics from a polyamide selective layer. This layer is formed on a microporous support by bringing together an aqueous phase containing an amine monomer (that often is aromatic) and an organic phase containing an aromatic acid chloride monomer (*9*). Typically, a diamine and trifunctional acid chloride are used to form a highly cross-linked polymer network (*10*). The reaction between the amine and the acid chloride is very fast (*11*) and forms the polyamide selective layer within seconds during the manufacturing process, effectively locking in the molecular structure of the membrane. Culp *et al.* directly charac-

Polyamide membrane density

Culp *et al.* used scanning transmission electron microscopy to image the highly heterogeneous selective polyamide layer of reverse-osmosis membranes. They combined these results with modeling studies to understand variations in water transport.



Thin but dense
The schematic shows that a thin but dense polyamide layer has limited water transport. The channels are obscured in this case.

Thick but less dense
The schematic shows that a thicker but less dense polyamide layer more readily transports water. The channels are visible in this case.

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terize membrane thickness and couple that information with density at the nanoscale. They used scanning transmission electron microscopy with a high-angle annular dark-field detector (HAADF-STEM) to provide a measure of a critical aspect of membrane structure at length scales relevant for describing small-molecule transport. This three-dimensional spatial information revealed where the polymer is (and is not) concentrated, which is important for understanding how water traverses the membrane. Critically, this nanoscale density mapping does not rely on a priori structural assumptions about the membrane material, so the authors could model transport pathways without adjustable parameters. This analysis revealed where water passage occurs in the membrane and, importantly, where water passage is restricted (see the figure).

Conventional macroscopic modeling suggests that passage of water should decrease as the membrane becomes thicker. That is, water passage is restricted as the water is required to navigate a longer path through the membrane. For a material of uniform thickness and density, such behavior would be observed. In RO membranes, however, the nanoscale inhomogeneity in thickness and density observed by Culp *et al.* leads to a situation where water passage can actually increase as the average thickness of the membrane increases if there is a low average density and a narrow density variation. As such, a thick, more homogeneous, and less dense membrane can offer better transport than a thin, dense, heterogeneous one. This behavior, not predicted by conventional modeling, is satisfactorily explained when variations in density and thickness are considered. Notably, bulk average measures of water diffusivity and thickness do not satisfactorily describe the inhomogeneous system caused in part by the nonlinear dependence of water passage on density and thickness.

The approach reported by Culp *et al.* represents a fundamentally different way to characterize RO membranes. The observation that surface-density distributions are important for water passage suggests that this approach may be useful for informing the design of, and directly measuring the impact of, antifouling coatings or other membrane surface treatments that are commonly used to prevent biofouling or reduce membrane degradation. Additionally, the microporous supports used in RO membrane manufacturing have been recognized to be critical for determining the ultimate properties of the membrane, and this technique could provide a direct measure of how microporous supports direct the formation of RO membranes during the interfacial polymerization process.

Physical aging or degradation processes can affect long-term material performance of membranes and polymers. For example, when glassy polymers are used in membranes, their properties change over time as the polymer relaxes toward equilibrium (*12*), and polyamide-based RO membranes are known to degrade in the presence of chlorine (*2*), which is commonly used as a disinfectant. The approach reported by Culp *et al.* could answer fundamental questions about how RO membranes age, degrade, or both over time.

"Critically, this nanoscale density mapping does not rely on a priori structural assumptions about the membrane material..."

As Culp *et al.* note, complementary data for salt transport through polyamide materials are still needed to enable a full description of small-molecule passage in RO membranes. Although obtaining such data may not be trivial, the present studies suggest that it should be possible to comprehensively measure and describe small-molecule transport through RO membranes without the need for assumptions about polymer or membrane structure. As such, the HAADF-STEM technique could be a key step toward answering questions that have lingered for decades about how polyamide-based RO membranes function. ■

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STEM CELLS

Detecting oxygen changes in the lungs

Lung airway basal stem cells directly sense changes in oxygenation, driving lung regeneration

By **William Zacharias**

The lungs exist in a distinct environment of constantly changing oxygen concentrations. Resultant tissue hyperoxia and hypoxia cause substantial organismal stress, and cells have evolved specific pathways to respond to such changes. This is a particularly acute challenge to the lungs, where differences in the partial pressure of oxygen (Po_2) in the circulation and inspired air must be integrated to ensure appropriate cellular responses and maintain tissue homeostasis. On page 52 of this issue, Shivaraju *et al.* (*1*) characterize how airway basal stem cells sense and respond to hypoxia (low O_2 tension), driving expansion of solitary neuroendocrine (NE) cells that generate paracrine signals to improve airway regeneration in mice. These data demonstrate the complexity of the mechanisms underlying how the lungs respond to changes in tissue oxygenation after injury.

The Po_2 of ambient air is ~160 mmHg and decreases during its transit from the nasal orifice to the air sacs (alveoli) in the lungs, reaching 100 mmHg in the distal lung. The alveolar-arterial gradient and mixture of oxygenated and deoxygenated blood in alveolar venules lead to a systemic arterial Po_2 of 95 to 100 mmHg that is delivered to end organs (*2*). Assuming intact cellular metabolism, returning venous blood ranges in Po_2 from 40 to 50 mmHg. Under conditions of reduced inspired oxygen concentration, such as high elevation, Po_2 is reduced throughout the lungs, causing regional vasoconstriction of pulmonary vasculature to match ventilation and perfusion within the most-oxygenated alveoli, a phenomenon called hypoxemic pulmonary vasoconstriction. As arterial Po_2 falls, specialized oxygen-sensing cells in the arterial carotid body and airway

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Geoffrey M. Geise

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