is required for the generation of a T_H2 response, which cells located in the vicinity of DC-dependent T cell activation produce the IL-4?

A different explanation for the initiation of CD4 T cell responses is provided by the study of Rissoan *et al.* The investigators (*4*) report that DCs exist in at least two forms: myeloid-like cells (DC1) produce abundant IL-12 and induce a T_H1 response, and lymphoid-like cells (DC2) induce a T_H2 response (see the figure). Not surprisingly, the lymphoid-like DCs secrete very low levels of IL-12, providing a permissive environment for T_H2 generation. Yet intriguingly, these DC2 cells fail to secrete IL-4. In this model, the CD4 T cell cytokines induced by DCs differ because the two types of DCs themselves differ in the inductive signals they provide to newly activated CD4 T cells. Most importantly, the induction of T_H2 responses described in this report is not only independent of IL-12 but also of IL-4, suggesting that there is a unique signal provided by DC2 that induces naïve T cells to become T_H2 cells.

These studies suggest a new function for DCs: determining which type of T cell immune response is generated. To do this, DCs must exist as functionally distinct subsets that are distinguished through morphology and the expression of cell surface glycoproteins. Both DC subsets retain the ability to activate naïve T cells, but differ in the delivery of cytokines or signals influencing CD4 T cell differentiation and functional commitment. The differences between the DC subsets appear to be a consequence of early maturation events. What is not known from the Rissoan study is whether the two types of DCs originate from the same precursor cells or whether the same precursor is influenced by its microenviroment to give rise to distinct subsets. (In this study, DC1 and DC2 were generated in vitro in the presence of distinct maturing cytokines.)

Selective T_H1 or T_H2 activation is crucial to the outcome of many immune responses. The findings of Rissoan and co-workers (*4*) now suggest that the responsibility for this decision be shifted from the T cell to the antigen-presenting cell. This, in turn, raises more questions: Which molecules induce T_H2 responses during contact between T cells and DCs? What distinguishes DC1 from DC2? Is it their microenvironment, as suggested by the recent study of Stumbles *et al.* (*7*), or is it the distinct invariant receptors used to ingest antigen by immature DCs in peripheral tissues? The focus of future research will now shift from the control of T cell activation to the control of DC1 and DC2 production. Intriguingly, the results of Rissoan *et al.* also indicate that T helper cells themselves may regulate T_H1 and T_H2 responses by determining the survival of the appropriate dendritic cell subset.

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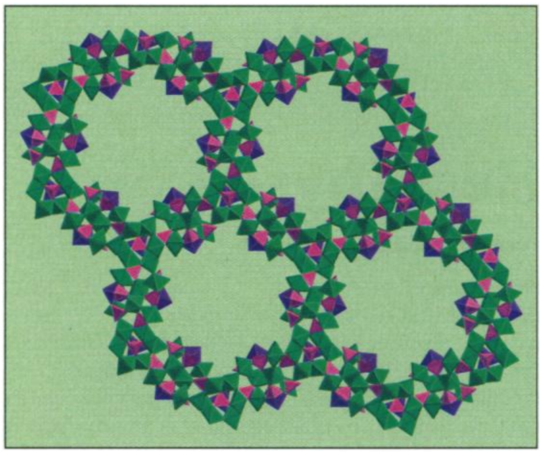
PERSPECTIVES: POROUS MATERIALS

Prospects for Giant Pores

Gérard Férey and Anthony K. Cheetham

The world of crystalline porous materials has long been dominated by aluminosilicate zeolites, which are used widely in catalysis, separations, and ion-exchange processes (*1*). The discovery of new families of porous materials, including new crystalline systems as well as amorphous mesoporous materials, has raised hopes that such materials could be tailored for new applications, for example, in sensors and nanotechnology. Consequently, there has been tremendous interest in novel porous solids, both inorganic and organic (*2*).

To date, more than 40 elements have been incorporated as major components in crystalline porous materials. Researchers seek even further diversity by increasing the size of their pores. Zeolites typically have pore diameters of less than 10 Å. Larger, "giant" pores might be used, for example, as nanoreactors, and may allow attachment of different chemical groups to their walls. An elegant natural material of this class is the iron phosphate mineral cacoxenite, which has channels 14 Å in diameter (see the figure) (*3*). Two eye-catching reports in this issue on pages 1145 and 1148 illustrate exciting synthetic design strategies being used for creating large-pore inorganic (*4*) and metallo-organic systems (*5*).



Ahead of the game? Cacoxenite, a natural iron phosphate mineral, has one of the largest pore sizes of the known crystalline nanoporous materials, but recent synthetic materials are surpassing its pore size (*4*).

It has been said that "Nature hates vacuum". This is certainly true in many solids with potentially very large cavities: The empty space is often filled by guest species or by interpenetration of identical sublattices. Different strategies can be used to circumvent this problem. Li *et al.* (*4*) use the templated "secondary building unit" (SBU) strategy to build up porous solids based on indium sulfide. SBUs are the structural components that create the architecture of the open framework. Large SBUs can be constructed from smaller units, for example, by assembling 4 or 10 tetrahedral units into supertetrahedral units, which then replace the single tetrahedra of the parent structures, resulting in much larger pores. Li *et al.* obtain open frameworks with a wall composition of $In_{10}S_{18}^{6-}$. The cavities are filled with charge-compensating organic cations and water molecules (*4*). Depending on the organic cation, two different architectures are found, named ASU-31 and ASU-32. The strategy is not new, but its use by Li *et al.* leads to structures with remarkably large cavities, with diameters of 25.6 and 14.7 Å for ASU-31 cages and ASU-32 tunnels, respectively. In both phases, the framework corresponds to only ~20% of the total volume, far below the ~40% found in other solids with large pores, such as cacoxenite and the zeolite faujasite.

Chui *et al.* (*5*) use metallo-organic polymers (*6*) to synthesize a material with large pores, which they name HKUST-1. In this

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supramolecular approach, functionalized organic molecules (here, benzene-1,3,5-tricarboxylic acid) bind to molecular inorganic species to form the three-dimensional network. The carboxylate groups lead to the formation of dimeric building units that condense to form a neutral three-dimensional system with channels 10 Å in diameter, occupied by loosely bound water molecules.

One of the main reasons that the aluminosilicate zeolites have been so widely exploited for commercial applications is that their structures tend to be stable, even in the absence of pore-filling molecules such as solvent molecules and organic cations. Their porosity can thus be used in applications such as catalysis and separations. Furthermore, their cavities often facilitate high mobility of simple cations, such as alkali metal ions, leading to their use for ion-exchange processes. Other classes of open-framework materials often collapse in the absence of pore-filling species and rarely exhibit high ionic mobility. In these respects the ASU and HKUST materials distinguish themselves. When HKUST-1 is heated to ~100°C, loss of water from the cavities leads to a material that is stable to ~250°C, with a large surface area and an accessible porosity of ~40%. Moreover, the channels can be lined with functional groups by replacing the water ligands with pyridine. In the ASU materials, the organic cations filling the cavities can be exchanged readily for simple metallic cations such as sodium and additional water. The adsorption properties of the resulting compounds, if they remain stable after the solvent is removed, may be extremely interesting. Furthermore, the ASU frameworks are semiconducting, in contrast to the insulating aluminosilicate zeolites, offering the possibility of interesting electronic applications.

Both of these studies significantly increase the possibilities for obtaining giant pores, but they also pose many questions. At which pore size do nanoporous solids with ordered walls give way to "mesoporous" compounds with disordered walls? The previous barrier at 20 Å is surpassed in ASU-31. A related question regards the size limit for clusters used as SBUs. Polyoxometalates and the giant molybdenum wheels described by Muller (*7*) may be thought of as very large potential SBUs, and three-dimensional networks of these building units could result in even larger cavities than those described here.

The metallo-organic synthesis route seems to be particularly versatile, because the nature and coordination of the inorganic species, the shape, dimensions, and the composition of the linkers, and the choice of their terminal ligands can all be varied. Here, the main difficulty probably lies in controlling the dimensionality of the resulting structures. Depending on the temperature and the nature of the solvent, the reaction products can span molecular, chain, lamellar and three dimensional architectures for the same species. To understand this, the species that exist under reaction conditions in the hydrothermal solution must be identified, and the mechanisms by which they form the final structure elucidated. In situ experiments, mainly by nuclear magnetic resonance spectroscopy and synchrotron x-ray diffraction, have provided significant insights into the formation of microporous compounds with small SBUs (*8*). Recent experiments have resulted in materials with larger and larger pores, but further insights into the formation process are essential if we are to design such materials. A knowledge of the species involved in the formation process could be combined with computer simulations to tune the topologies of porous solids.

Well-ordered crystalline solids with giant pores remain quite rare. The discovery of such materials in two quite different chemical systems (*3, 4*) illustrates the scope of this rapidly expanding area. The possibilities that they offer, the different synthesis strategies that they use, and the modulation of the sizes and chemistries of the pores that they imply underline the potential for further exciting results in this important field.

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PERSPECTIVES: NEUROBIOLOGY

Brain, Heal Thyself

Daniel H. Lowenstein and Jack M. Parent

In 1913, the great Spanish neuroscientist Santiago Ramón y Cajal concluded a treatise entitled *Degeneration and Regeneration of the Nervous System* by declaring, "In adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated" (*1*). This assertion, based on Cajal's meticulous study of changes in brain anatomy after injury, has been the prevailing dogma for nearly a century. We are still taught that the fully mature brain lacks the intrinsic mechanisms needed to replenish neurons and reestablish neuronal networks after acute injury or in response to the insidious loss of neurons seen in neurodegenerative diseases.

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It is time to lay to rest the dogmatic assumption that the central nervous system (CNS) of adult mammals cannot repair itself. Obviously, CNS injuries such as stroke, trauma, or neurodegenerative processes do not fully reverse themselves spontaneously. Recent work suggests, however, that the mammalian CNS has a much greater potential for producing new neurons and repairing damaged regions than previously thought.

First and foremost, the mature CNS is not as hostile an environment for the regeneration of neuronal networks as once believed. It has been known for decades that, in a variety of mammalian species, specific populations of CNS neural progenitors normally proliferate well into adulthood (*2*). In rodents, for example, progenitor cells adjacent to the cerebral ventricles give rise to neurons that migrate rostrally to reside within the olfactory bulb (see the figure) (*3*). Similarly, a pool of progenitor cells within the dentate gyrus of the hippocampus, a structure important for learning and memory, continues to produce new dentate granule cells throughout life. This phenomenon even occurs in the brains of primates, including humans (*4*).

Not only does this neuronal birth continue into adulthood, but the newly born cells are able to migrate throughout the granule cell layer, and they can extend intricate axon arbors hundreds of micrometers away into the farthest reaches of their normal targets (*5*). Neural progenitors transplanted into the CNS of an adult recipient have the ability to survive, differentiate, and become incorporated (*6*). Furthermore, the mature CNS continues to express a variety of molecules that are required for the formation of neuronal networks during embryonic development. These include growth fac-

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