Silicon Siting

The synthesis of many pharmaceutical and agrochemical compounds requires selective functionalization of multiple different sites on aromatic ring frameworks. The size and electronic properties of the first substituent added can influence where the next one is likely to end up. Cheng and Hartwig (p. 853, see the Perspective by Tobisu and Chatani) discovered a rhodium-catalyzed reaction that is particularly sensitive to size to place a silicon substituent as far away as possible from the largest group already on the ring. The silicon group can then be replaced with carbon, oxygen, nitrogen, or halide substituents as needed.

Fear, Memory, and Place

Contextual fear conditioning (CFC) is widely used as a hippocampal-dependent classical conditioning task to model human episodic memory. Lovett-Barron et al. (p. 857) combined in vivo imaging with pharmacology, pharmacogenetics, and optogenetics and they found that somatostatin-expressing, dendrite-targeting γ-aminobutyric acid–releasing interneurons in hippocampal area CA1 are required for CFC. During CFC, sensory features of the aversive event reach hippocampal output neurons through excitatory cortical afferents and require active inhibitory filtering to ensure that the hippocampus exclusively encodes the conditioned stimulus.

A 3D Graphene?

Discoveries of materials with exciting electronic properties have propelled condensed matter physics over the past decade. Two of the best-known examples, graphene and topological insulators, have something in common: a linear energy-momentum relationship—the Dirac dispersion—in their two-dimensional (2D) electronic states. Topological insulators also have a more mundane aspect of their electronic structure, characterized by a band gap. Another class of materials, topological Dirac semimetals, has been proposed that has a linear dispersion along all three momentum directions—a bulk Dirac cone; these materials are predicted to have intriguing electronic properties and to be related to other exotic states through quantum phase transitions. Liu et al. (p. 864, published online 16 January) detected such a state in the compound Na$_3$Bi by using photoemission spectroscopy.

Optimizing Injectable Hydrogels

Injectable hydrogels are showing promise as scaffolds in regenerative medicine because they can be injected in liquid form and transform in situ into the gel state. However, when exposed to ionic solutions, such as those found in the body, hydrogels can increase in volume by a factor of 2, which can weaken the material. Kamata et al. (p. 873) added a thermoresponsive component to a hydrogel so that the thermoresponsive component would tend to collapse in shape when heated and counteract the hydrogel’s tendency to swell. Indeed, the resulting gel retained its unswollen volume following immersion in a physiological solution and retained its mechanical strength during repeated stretching or compression.

Toward an Artificial Muscle >>

In designing materials for artificial muscles, the goals are to find those that will combine high strokes, high efficiency, long cycle life, low hysteresis, and low cost. Now, Haines et al. (p. 868; see the Perspective by Yuan and Poulin) show that this is possible. Twisting high-strength, readily available polymer fibers, such as those used for fishing lines or sewing thread, to the point where they coil up, allowed construction of highly efficient actuators that could be triggered by a number of stimuli.

Toward Successful Tissue Repair

The therapeutic use of growth factors in tissue regeneration has suffered from safety and efficacy issues. Reasoning that the unmet potential may be because of nonphysiological delivery, Martino et al. (p. 885) engineered growth factors to bind strongly to extracellular matrix proteins. These variants were able to induce superior tissue repair, compared to the wild-type proteins. Furthermore, unwanted side effects were decreased: For example, the engineered angiogenic growth factor VEGF showed reduced vascular permeability, a concern that has limited the therapeutic efficacy of wild-type VEGF.

Two-Faced Viral Protein

Flaviviruses cause human diseases such as West Nile fever and dengue fever. The flavivirus nonstructural protein 1 (NS1) has multiple functions in flavivirus biology and is a target for vaccine development. Dimeric NS1 is essential for replication of the viral genome inside host cells, while hexameric NS1 is secreted and plays a role in evasion of the immune system. Akey et al. (p. 881, published online 6 February; see the Perspective by Shi) report crystal structures for full-length glycosylated NS1 from West Nile and dengue viruses. The structures show a hexamer comprised of three dimers. The structural analysis together with liposome and mutational studies identify a membrane interacting surface on one face of the dimer and an immune evasion surface on the other.

Oops, That’s Not Right…

Evaluating our actions, and detecting our errors, is crucial for adaptive behavior. These fundamental executive functions are intensively studied in cognitive and social neuroscience, but their anatomical basis remains poorly characterized. Using intracerebral electroencephalography in patients being prepared for epilepsy surgery, Bonini et al. (p. 888) found that, contrary to what is widely assumed, the supplementary motor area, and not the anterior cingulate cortex, plays a leading role in these processes. The data provide a precise spatio-temporal description of the cortical network underlying action monitoring and error processing.
Robust to Change

The variation in genetic sequences determining the binding of transcription factors is believed to be an important facet of evolution. However, the degree to which a genome is robust, that is, able to withstand changes and how robustness affects evolution is unclear. Payne and Wagner (p. 875) investigated the empirical support for mutational robustness by examining transcription factor (TF) binding in the mouse and yeast genomes. A network analysis of the degree of variation revealed that the sites with the highest affinity for TF binding exhibit the greatest tolerance for nucleotide substitutions, whereas low-affinity sites exhibit greater sensitivity to mutation. Thus, while mutational robustness and evolvability are antagonistic at the genotypic level, they are synergistic at the phenotypic level.

Morphogen Pipeline

Developmental effects of morphogens are often thought to result from release of such signaling proteins from a cell, which then diffuse away to act by binding to receptors on distant target cells. But evidence is accumulating that another mechanism exists for such communication. Endothelial cells in the fruit fly have long, skinny extensions that reach away from cells for long distances, and these “cytonemes” can take up morphogens from adjacent cells. A key experiment to support a signaling role of such structures would be to show that disruption of cytonemes disrupts signal transduction. Roy et al. (p. 852, published online 2 January; see the Perspective by Rørth) provide such evidence and conclude that the fly morphogen known as decapentaplegic (a relative of transforming growth factor–β) must be transported through cytonemes to promote proper development of the trachea.

Catalysis in the Membrane

Enzymes in the UbiA superfamily of integral membrane proteins synthesize lipid-soluble aromatics such as ubiquinones and chlorophylls that function in energy storage and energy transfer in mitochondrial and chloroplast membranes. Cheng and Li (p. 878) report structures of an archaeal UbiA protein in both apo and substrate-bound states. The structures show a large active site with a lateral portal that is likely to give access to the long-chain isoprenoid substrates. The findings suggest a mechanism for substrate recognition and catalysis and can explain disease-related mutants in eukaryotic homologs.

Entorhinal Cell Clusters

There is considerable interest in understanding the function of neurons in layer 2 of the medial entorhinal cortex and how they generate their unique firing patterns, which are important in the recall of facts and past events (see the Perspective by Blair). Ray et al. (p. 891, published online 23 January) investigated principal cells in layer 2 by immunoreactivity, projection patterns, microcircuit analysis, and assessment of temporal discharge properties in awake, freely moving animals. In tangential sections, pyramidal neurons were clustered into patches arranged in a hexagonal grid—very similar to the patterns observed in grid cell spatial firing. These patches received selective cholinergic innervation, which is critical for sustaining grid cell activity. Kitamura et al. (p. 896, published online 23 January) found that these cells drive a hippocampal circuit by projecting directly to the hippocampal CA1 area and synapsing with a distinct class of inhibitory neurons. This circuit provides feed-forward inhibition in combination with excitatory inputs from layer 3 cells of the medial entorhinal cortex, projecting to CA1 pyramidal cells to determine the strength and time window of temporal associative inputs.