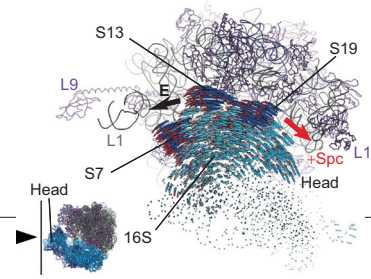
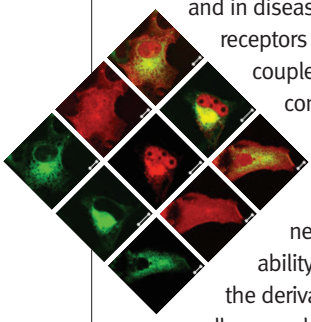
# In this ISSUE




## Inside GPCR Signaling

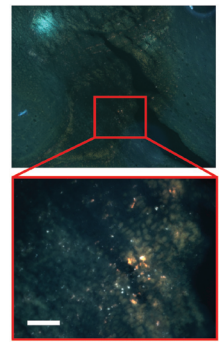
The hormone estrogen is known to signal through several cellular receptors. This undoubtedly contributes to its many roles in biology, such as reproductive development and bone formation, and in disease, such as cancer and osteoporosis. In addition to the nuclear estrogen receptors ERα and ERβ, estrogen signals through the 7-transmembrane G-protein-coupled receptor (GPCR) GPR30. However, Revankar *et al.* (p 536), prompted by conflicting reports of the localization of GPR30, create a series of estrogen derivatives to explore just where in the cell estrogen and GPR30 interact.



On the basis of previous data demonstrating the presence of GPR30 primarily in the endoplasmic reticulum, the authors synthesized several neutral and charged estrogen derivatives to investigate whether cell permeability is required for the interaction. Examination of the signaling capabilities of the derivatives, either by calcium mobilization or activation of PI3K, revealed that the cell-permeable derivatives were much more effective activators of GPR30 than the impermeable compounds. These results suggest that GPR30 can initiate signaling from an intracellular location, straying from the conventional wisdom that GPCRs function only at the cell surface.

## Illuminating Aβ

Deposition of aggregates of the peptide β-amyloid (Aβ) around neurons is considered to be the culprit in the pathogenesis of Alzheimer's disease (AD). Mature amyloid fibrils, as well as immature or alternate Aβ aggregates of different morphologies, have all demonstrated toxicity, but the mechanism of aggregate formation and the correlation between aggregate structure and toxicity are not well-understood. Nilsson *et al.* (p 553 and Point of View p 525) use luminescent conjugated polymers (LCPs) to explore the structural characteristics of various Aβ fibril conformations.



LCPs are polymers composed of polythiophene backbones with varying ionic side chains. In contrast to other dyes used for detecting Aβ, LCPs contain a flexible thiophene backbone that affects their spectral characteristics. Because LCP conformation will vary depending on the conformation of the protein to which it is bound, a spectral signature for different protein conformations can be generated. The authors demonstrate that LCPs can be used both *in vitro* and in the brain tissue of mouse models of AD to distinguish between various conformations of Aβ. These innovative tools can provide both structural and mechanistic insight into the deleterious effects of various Aβ aggregates.

## A Real Head-Turner!

Antibiotics that are able to resist the emergence of resistant bacterial strains are of growing importance in the clinic. In addition, the mechanisms underlying their ability to ward off resistant strains could facilitate the design of improved medicines. Spectinomycin, an antibiotic used to treat gonorrhea, inhibits protein synthesis by preventing translocation of transfer RNAs and messenger RNAs (mRNA) on the ribosome. Borovinskaya *et al.* (p 545) use structural and biochemical studies to elucidate the surprising molecular details behind spectinomycin's powerful mechanism of action.

Spectinomycin is known to bind to a helix located in the "head" of the 30S ribosomal subunit. Current models of protein translocation along the ribosome suggest that, after a ratchet-like motion of the 30S subunit relative to the 50S subunit, the 30S subunit undergoes a conformation change in which the head swivels. X-ray crystallography of spectinomycin bound to the 70S ribosome suggested that spectinomycin keeps the head from swiveling. Biochemical translocation experiments provided further evidence that the resulting conformation change affects mRNA movement on the ribosome.

## Tinkering with Transcription

Hypoxia, a deficiency in oxygen, is involved in normal physiological processes such as programmed cell death but can also promote pathological processes such as the progression of cancer. Under hypoxic conditions, the transcription factor hypoxia inducible factor (HIF-1) activates several genes that help cells adapt to reduced oxygen. To facilitate dissection of the HIF-1-inducible pathways that contribute to normal *versus* pathological processes, Nickols *et al.* (p 561) compare three approaches for controlling HIF-1-induced gene expression.

The authors disrupted the interaction between HIF-1 and DNA using DNA-binding polyamides, which can be programmed to bind specific sequences of DNA, the DNA-binding natural product echinomycin, or a small interfering RNA (siRNA) targeted against HIF-1α. Microarrays were used to assess the global effects of these molecules on hypoxia-induced gene expression. It is interesting that a specific polyamide affected only a subset of hypoxia-induced genes, whereas the siRNA and the echinomycin affected the expression of nearly all genes induced by hypoxia. These results suggest that polyamides may be programmed to manipulate hypoxia-induced pathways that lead to disease progression.

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