Highlights from Early Edition

Selected articles appearing the week of October 1, 2012

Highlights from Early Edition

- **Early Edition Table of Contents**
- **PNAS in the News**
- **Press Information**

New for October 5, 2012

Neuroscience

- Visual neurons acquire selectivity when searching for patterns

Recent Highlights

Biochemistry

- How DNA mismatch repair proteins find their targets
- Unraveling the complications of a biological clock

Developmental Biology

- Spatial patterns of gene expression during development

Environmental Sciences

- Microbial taxa in deep-sea sediment linked to geochemical variations

Genetics

- Inherited risk of testicular cancer

Medical Sciences

- Drug class protects against ALS and Parkinson in mouse, worm models
- Scientific misconduct to blame for many retractions in the life sciences
- Neuronal nitric oxide initiates and maintains penile erection

Medical Sciences, Chemistry

- VEGFR TK inhibitor efficacy depends on conformational differences

Microbiology

- Antiviral immune response in mosquitoes
- X-ray structures suggest role for bat influenza NA proteins
- Detoxification of singlet oxygen reveals core marine metabolic process

Neuroscience

- Parallel Alzheimer's treatments suggest

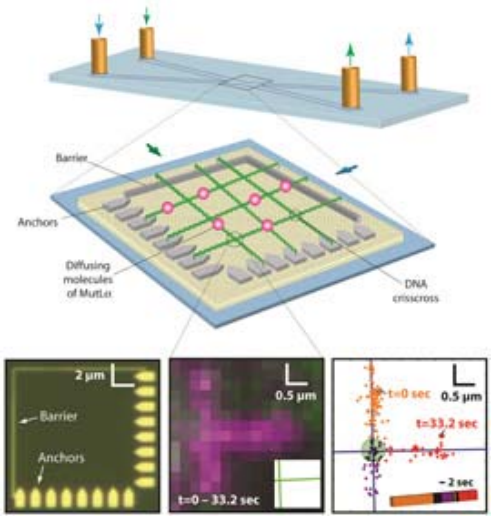
single therapeutic target

Psychological and Cognitive Sciences

- Exploring gender bias in academic science

Biochemistry

How DNA mismatch repair proteins find their targets



DNA curtains allow visualization of protein transfer.

"Single-molecule imaging reveals target-search mechanisms during DNA mismatch repair"
by Jason Gorman, et al.
[Abstract]

Proteins have the ability to locate specific targets on DNA, but how they do so remains poorly understood. Jason Gorman et al. used single-molecule microscopy to visualize the postreplicative mismatch repair (MMR) proteins MutSα and MutLα, which correct errors in DNA synthesis, as they search for their DNA targets. The researchers used total internal reflection fluorescence microscopy (TIRFM) and nanofabricated DNA curtains—DNA strands anchored to a lipid bilayer —containing mismatches to observe as MutSα searched for DNA mismatches and MutLα found the mismatch-bound MutSα. The researchers found that MutSα can find mismatched bases either through 1D sliding over the DNA, or 3D diffusion. MutLα located the mismatch-bound MutSα either by 1D hopping over stretches of DNA or by 3D transfer between juxtaposed DNA segments. The mismatch-bound MutSα/MutLα complex was released upon ATP-binding, and scanned the flanking DNA by 1D-diffusion. The researchers also found that upon release from a mismatch, MutSα is altered so that it no longer targets mismatches, preventing it from binding again to the same site of DNA damage. The study provides a direct visualization of how MMR proteins use different modes of diffusion to recognize and repair damaged DNA, according to the authors. – S.R.

Biochemistry

Unraveling the complications of a biological clock

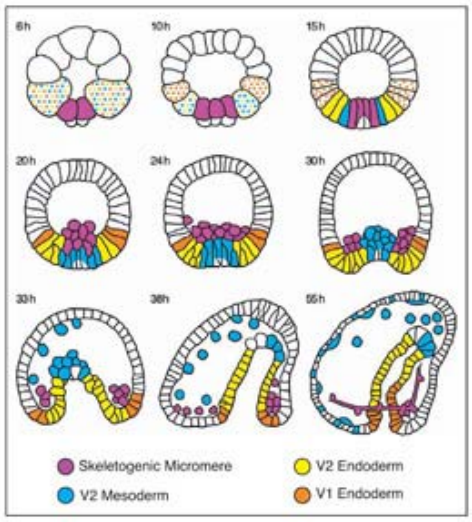
Circadian clocks, which control biological rhythms in tune with daily changes in ambient light and temperature, are composed of proteins called oscillators. Cyanobacterial oscillators consist of three proteins, KaiA, KaiB, and KaiC, whose interactions generate self-sustained 24 h biochemical rhythms. Yong-Gang Chang et al. performed a biochemical analysis of the clock proteins of the cyanobacterium *Thermosynechococcus elongatus* to uncover the molecular workings that drive the oscillator. Though researchers previously showed that the cyanobacterial oscillator can be reconstituted in a test tube by mixing the three proteins in the presence of the chemical compound ATP, the cellular energy currency, the oscillator's precise mechanism remains elusive. The authors report that rhythmic stacking between two ring-shaped structures called CI and CII, both found in the KaiC protein, propels the oscillator clockwise. In addition, the authors found that ring stacking explains how the chemical compound ADP, a naturally
occurring cellular derivative of ATP, can reset the clock. According to the authors, rhythmic ring stacking and unstacking together provide an explanation for circadian clock function, implicated in a range of human diseases. – P.N.

Pocket chronograph. Paul Buhre. Le Locle, Switzerland. Image courtesy of shakko/Wikimedia.

"Rhythmic ring–ring stacking drives the circadian oscillator clockwise"
by Yong-Gang Chang, Roger Tseng, Nai-Wei Kuo, Andy LiWang
[Abstract]

Developmental Biology

Spatial patterns of gene expression during development



Sea urchin embryogenesis.

"Predictive computation of genomic logic processing functions in embryonic development"
by Isabelle S. Peter, Emmanuel Faure, and Eric H. Davidson
[Abstract]

During development, gene regulatory networks (GRNs) control the dynamic spatial patterns in which regulatory genes are expressed. As such, GRN models can potentially reveal system-level causal relationships during the developmental process. In their Feature Article, Isabelle Peter et al. transform a well-established GRN model into a predictive and dynamic Boolean computational model that computes spatial and temporal gene expression based on the regulatory logic and gene interactions for embryonic development in the sea urchin. During the initial 30 hours until the gastrula formed, the model predicted hourly expression patterns of numerous individual regulatory genes in four different spatial domains of the embryo, according to the authors, with remarkable spatial and temporal accuracy compared with direct observation. In addition, the authors used the model to perturb *in silico* regulatory functions and spatial patterns in the embryo and reproduced developmental abnormalities that matched experimental results. According to the authors, the study demonstrates that the adapted GRN model contains sufficient information to describe gene expression during the complex developmental process, and that the Boolean model can serve as a tool to test *in silico* regulatory connections and developmental perturbations. – T.J.

Environmental Sciences

Microbial taxa in deep-sea sediment linked to geochemical variations

Marine sediments host the largest reservoir of organic carbon and support the highest microbial abundance on Earth. Though the metabolic processes of these communities profoundly affect global biogeochemical cycles, the physiological activities of most subsurface microorganisms remain largely uncharacterized. Steffen Jorgensen et al. report that microbial community structure directly correlates to geochemistry, providing a means to determine factors that shape community composition and predict the metabolic properties of Earth's most abundant deep-sea sediment microbes. The authors generated an extensive geochemical dataset of microbial profiles from two Arctic Mid-Ocean Ridge system sediment cores and found correlations between changes in the relative abundance of taxonomic groups and geochemical variations. Four key geochemical parameters–total organic carbon, iron content, manganese content, and sulfate concentration in the pore water–were tightly linked to the taxonomic distribution of microorganisms, suggesting that organic carbon and mineral content likely drive microbial community structure and, conversely, community structure likely determines sulfate concentration. The findings help constrain the metabolic regimes of the most abundant prokaryotic organisms in marine sediments, and with further study may lead to models that can predict the long-term fate of carbon and other essential elements, according to the authors. — T.J.

Retrieving gravity core from the Arctic Spreading Ridge System. Image courtesy of the Centre for Geobiology, Bergen, Norway.

"Correlating microbial community profiles with geochemical data in highly stratified sediments from the Arctic Mid-Ocean Ridge"
by Steffen Leth Jorgensen, et al.
[Abstract] **OPEN ACCESS ARTICLE**

Genetics

Inherited risk of testicular cancer

While testicular germ cell tumors (TGCTs) rank third in heritability among all cancers, epigenetic effects related to maternal conditions are thought to affect susceptibility as much—or more than—genomic factors. Investigating a possible molecular mechanism for these effects, Vicki Nelson et al. examined the Deadend1 (*Dnd1*) gene that enhances TGCT susceptibility in mice, by in part interacting epigenetically with other TGCT modifier genes in previous generations. Noting that *Dnd1* shares sequence similarity with *Apobec1* complementation factor, a protein involved in RNA editing, the authors conducted experiments with a genetically engineered *Apobec1* deficiency in TGCT-susceptible mice. The experiments, the authors report, revealed that partial loss of *Apobec1* function conferred an increased TGCT risk in the paternal line that was inherited in a conventional manner. By contrast, partial loss suppressed TGCTs in the maternal line in both partially and fully deficient males, and significantly reduced TGCT risk in a transgenerational manner. The findings suggest that *Apobec1* critically impacts TGCT susceptibility in both a conventional and transgenerational manner, according to the authors. — T.J.

"Transgenerational epigenetic effects of the *Apobec1* cytidine deaminase deficiency on testicular germ cell tumor susceptibility and embryonic viability"
by Vicki R. Nelson, et al.
[Abstract]

Medical Sciences

Drug class protects against ALS and Parkinson in mouse, worm models

Prolonged administration of P7C3, a proneurogenic, neuroprotective aminopropyl carbazole, safely restores hippocampal structure and function to mice suffering from pathologically high levels of neuronal apoptosis in the dentate gyrus. Researchers have also known that administering P7C3 to aged rats impedes hippocampal cell death and enhances cognitive ability related to terminal aging. Two studies examine whether the demonstrated action of P7C3 can be extended to models of human degenerative brain disease. Rachel Tesla et al. provide evidence that P7C3A20, a highly active analog of P7C3, protects ventral horn spinal cord motor neurons from cell death in a mouse model of amyotrophic lateral sclerosis (ALS). When administered at disease onset, the authors report, reductions in cell death correlated with measurable improvements in motor function decline. In a related study, Héctor De Jesús-Cortés et al. found that P7C3 also protects mature neurons in brain regions outside of the hippocampus, and in particular, blocks the death of dopaminergic neurons in the substantia nigra of adult mice, an accepted model of Parkinson disease (PD). The authors show that P7C3 and P7C3A20 protect against the loss of dopaminergic neurons and preserve mobility in a *Caenorhabditis elegans* PD model, and in addition, demonstrate the hippocampal proneurogenic efficacy of four new P7C3 analogs. These four analogs, the authors report, also protected test subjects in a mouse model of PD. Both studies highlight the specific role of the P7C3 class of drugs by showing that Dimebon, an experimental antihistaminergic treatment with significantly weaker proneurogenic and neuroprotective properties, confers no protection in either the ALS or PD models. Taken together, the findings suggest that the chemical scaffold represented by P7C3 and P7C3A20 may provide a basis to discover and optimize future pharmacologic agents aimed at treating human neurodegenerative diseases such as ALS and PD, according to the authors. — T.J.

"Neuroprotective efficacy of aminopropyl carbazoles in a mouse model of amyotrophic lateral sclerosis"
by Rachel Tesla, et al.
[Abstract] **OPEN ACCESS ARTICLE**

"Neuroprotective efficacy of aminopropyl carbazoles in a mouse model of Parkinson disease"
by Héctor De Jesús-Cortés et al.
[Abstract] **OPEN ACCESS ARTICLE**

Medical Sciences

Scientific misconduct to blame for many retractions in the life sciences

Retraction of flawed scientific publications is an important part of the scientific process, serving to correct the scientific literature. Ferric Fang et al. conducted a comprehensive review of retracted biomedical and life sciences research articles listed in the PubMed database and found that approximately two-thirds of these retractions were due to some form of misconduct. Of the retractions studied, 43.4% were retracted due to fraud or suspected fraud, 14.2% due to duplicate publication, 9.8% due to plagiarism, and the rest were retracted because of miscellaneous or unknown reasons. The percentage of scientific articles retracted due to fraud has increased approximately 10–fold since 1975, with a smaller increase in retractions due to error, the authors report. The United States, Germany, Japan, and China accounted for three–quarters of retractions due to fraud or suspected fraud, while China and India accounted for the majority of retractions due to plagiarism and duplicate publication, the study suggests. Retractions due to fraud or error were associated with journals with significantly higher impact factors compared with retractions due to plagiarism and duplicate publication. Scientific misconduct appears to have played a more prominent role in retractions in the biomedical literature than previously thought, according to the authors. — S.R.

"Misconduct accounts for the majority of retracted scientific publications"
by Ferric C. Fang, R. Grant Steen and Arturo Casadevall
[Abstract]

Medical Sciences

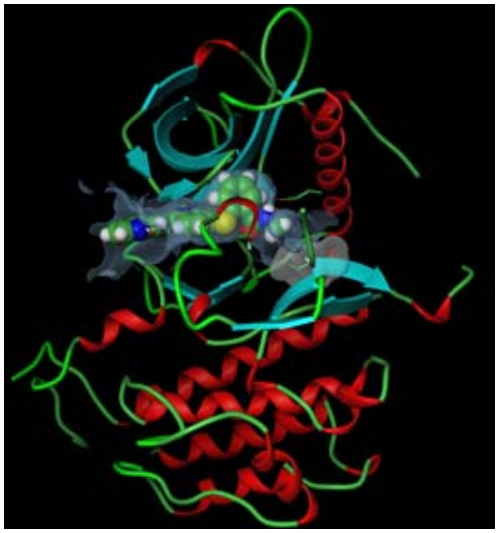
Neuronal nitric oxide initiates and maintains penile erection

Nitric oxide (NO) generated by neuronal NO synthase (nNOS) is an established mediator of penile erection. Though nNOS is closely tied to penile innervation, NO signaling is thought to initiate erection but not participate in the sustained erection required for normal sexual performance. K. Joseph Hurt et al. show that cyclic adenosine monophosphate (AMP)-dependent protein kinase (PKA) phosphorylates nNOS at serine (S)1412 and mediates erectile physiology, including sustained erection. Using a specially designed antibody that selectively recognizes nNOS phosphorylated at S1412, the authors show that electrically stimulating penile innervation in rats increases S1412 phosphorylation, and that PKA inhibitors block this response. In addition, the authors found that forskolin (FSK), a drug commonly used in the laboratory to increase intracellular cyclic AMP, also activates nNOS phosphorylation. In further trials with mice, the authors report, nNOS deletion or treatment with a known NOS inhibitor prevented sustained erection, either elicited by FSK injection or augmented by FSK during electrical stimulation. Taken together, the findings strongly suggest that nNOS both initiates and helps maintain penile erection, offering a therapeutic target for treating erectile dysfunction, according to the authors. — T.J.

"Cyclic AMP-dependent phosphorylation of neuronal nitric oxide synthase mediates penile erection"
by K. Joseph Hurt, et al.
[Abstract]

Medical Sciences, Chemistry

VEGFR TK inhibitor efficacy depends on conformational differences



Crystal structure of VEGF receptor tyrosine kinase.

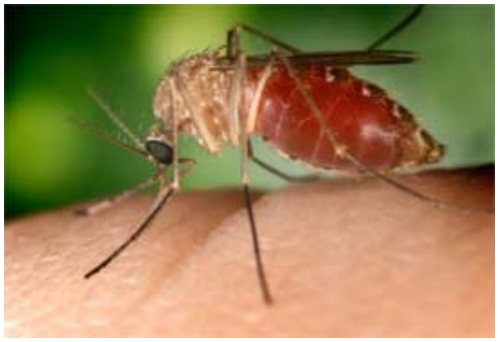
"Molecular conformations, interactions and properties associated with drug efficiency and clinical performance among VEGFR TK inhibitors"
by Michele McTigue, Brion W. Murray, Jeffrey H. Chen, Ya-Li Deng, James Solowiej, and Robert S. Kania
[Abstract] **OPEN ACCESS ARTICLE**

Anticancer drugs known as tyrosine kinase (TK) inhibitors block critical TK activity and disrupt vascular endothelial growth factor receptor (VEGFR) signaling. Four structurally diverse VEGFR TK inhibitors have been approved to treat renal cell carcinoma, a cancer that has been linked to aberrant VEGF signaling; however, the therapies' distinct clinical efficacies and VEGF-related safety profiles suggest that each inhibits its shared molecular target differently. In their Feature Article, Michele McTigue et al. determined the potencies, time-dependence, selectivities, and X-ray structures of drug—kinase complexes for the VEGFR TK inhibitor class and found unique drug—kinase interactions that correspond to differences in potency and ligand efficiency. According to the authors, distinct conformations of the juxtamembrane region, a key VEGFR TK regulatory domain, fundamentally underlie the performance differences. In addition, the authors determined that the identified drugkinase structural interactions explain trends in in vitro measurements that translate well to clinical performance. The findings, which result from a detailed, side-by-side comparison of molecular interactions within a single drug class, demonstrate a principle that can be used to optimize the in vivo performance of future therapies, according to the authors. – T.J.

Microbiology

Antiviral immune response in mosquitoes

The human response to infection by West Nile virus (WNV) and other mosquito-borne diseases has been extensively studied, but less is known about the insect immune pathways that restrict viral infection in mosquitoes. Using a cell line derived from the *Culex quinquefasciatus* mosquito, a known WNV vector, Prasad Paradkar et al. studied the function of *Cx*Vago, the mosquito ortholog of an antiviral peptide first identified in fruit flies. The authors discovered that *Cx*Vago was upregulated following WNV infection through a mechanism that required Dicer-2, a ribonuclease involved in the insect RNAi pathway and an important component of the insect antiviral response. The authors further demonstrated that *Cx*Vago is secreted from WNV-infected cells and restricts WNV infection by activating the Jak-STAT signaling pathway, an evolutionarily conserved pathway that regulates the expression of immune system genes in vertebrates in response to proteins called interferons, which signal the presence of pathogens. Although Vago shares no structural homology with interferons, the authors suggest that it may function as an interferon-like signaling molecule, enabling cell-to-cell communication of an innate antiviral response in insects. The findings
may aid the development of strategies to disrupt mosquito-borne disease transmission, according to the authors.— N.Z.



Culex quinquefasciatus mosquito, a known vector for the West Nile virus. Image courtesy of the CDC/Jim Gathany.

"Secreted Vago restricts West Nile virus infection in *Culex* mosquito cells by activating the Jak-STAT pathway"
by Prasad N. Paradkar, et al.
[Abstract]

Microbiology

X-ray structures suggest role for bat influenza NA proteins

Researchers recently described the bat influenza A virus H17N10, whose neuraminidase (NA) gene encodes a protein that appears to have sharply diverged from all known influenza NAs. In the current issue, two studies extend this work by presenting X-ray structures for NA proteins from the H17N10 bat influenza virus. Xueyong Zhu et al. examined NA proteins expressed from two H17N10 subtypes and found that although the overall structure is highly conserved, the active site differs substantially from known influenza A NA subtypes and influenza B NA. In particular, most amino acid residues required for NA activity are substituted, resulting in a wider active site due primarily to displacements in the 150-loop. These structural alterations, the authors report, and an observed absence of NA activity, suggest that N10 NA proteins function differently than NA proteins in other influenza viruses can be accurately characterized as NA-like. In a parallel study, Qing Li et al. solved the crystal structure of N10 from H17N10 bat influenza virus and identified key alterations to the structure and function of the 150-loop. Substituted residues in the active site, the authors determined, are poorly equipped for binding or cleaving terminally linked sialic acid receptors, and in vitro enzymatic assays demonstrated that N10 lacks canonical NA activity. Moreover, the authors observed residues 147–152 participating in intermolecular interactions unrelated to known NA activity. These key differences in active site residues, according to the authors, may help explain why N10 NA does not function like other influenza viruses and suggest that current NA inhibitors may not be effective against pathogenic bat influenza. Together, these studies offer important insights and raise new questions about the structure and function of known influenza A viruses and the future of the H17N10 as a potential human pathogen, according to the authors. – T.J.

"Crystal structures of two subtype N10 neuraminidase-like proteins from bat influenza A viruses reveal a diverged putative active site"
by Xueyong Zhu, et al. [Abstract]

"Structural and functional characterization of neuraminidase-like molecule N10 derived from bat influenza A virus"
by Qing Li, et al. [Abstract]

Microbiology

Detoxification of singlet oxygen reveals core marine metabolic process

Chlorophyll *a* (Chl-*a*), pheophytin *a* (Phe-*a*), and cPPB-*a*E under white (*Top*) and UV (*Bottom*) light.

"Ubiquity and quantitative significance of detoxification catabolism of chlorophyll associated with protistan herbivory"
by Yuichiro Kashiyama, et al.
[Abstract] **OPEN ACCESS ARTICLE**

Virtually all life on Earth depends on chlorophyll, the biomolecule by which photosynthetic organisms convert photons into the chemical potentials that drive metabolic processes. But chlorophylls can also generate singlet oxygen, causing severe cellular damage. In a Feature Article, Yuichiro Kashiyama et al. explore how these critical components of the Earth ecosystem avert the threat of phototoxicity. The authors examine how photosynthetic organisms in aquatic ecosystems break down singlet oxygen and identify a previously unreported process of chlorophyll detoxification. By conducting feeding experiments on several microorganisms to screen for detoxified chlorophyll catabolites, the authors found that heterotrophic protists, after ingesting algae, accumulate 13^2,17^3-cyclopheophorbide *a* enol (cPPB-*a*E). Due to its inability to generate singlet oxygen in vitro, the authors suggest, cPPB-*a*E qualifies as a detoxified catabolite of chlorophyll *a*. The authors further demonstrated that cPPB-*a*E is ubiquitous in aquatic environments and is often the predominant chlorophyll *a* derivative. The findings suggest a critical role for cPPB-*a*E metabolism in aquatic ecosystems, linking microscopic primary producers to the macroscopic food web and influencing modern oceanic carbon cycling and sequestration, according to the authors. – T.J.

Neuroscience

Visual neurons acquire selectivity when searching for patterns

Visual cortical neurons respond to certain features of objects, such as color, orientation, and shape. Known as selectivity, this ability to key on specific patterns usually manifests in the initial spike of the neurological response, suggesting that the visual cortex is largely hard-wired for a wide range of stimuli. In Michael Goldberg's Inaugural Article, Anna Ipata et al. show that V4 visual neurons in monkeys develop selectivity for a sought-after pattern when the task requires distinguishing between patterns in the visual field. According to the authors, when test subjects were required to search for a capital "T" among variously oriented lowercase "t" distractors, V4 neurons became selective for the target approximately 40 ms after selectivity appeared for basic pattern features like orientation and color. However, when locating the object in space required simply turning by a specified amount, V4 neurons did not distinguish the search target from the distracters, the authors report. The findings suggest that the brain uses a late-developing selectivity for tasks that require "feature attention" or searching within the receptive field, according to the authors. — T.J.

"Feature attention evokes task-specific pattern selectivity in V4 neurons"
by Anna E. Ipata, Angela L. Gee, and Michael E. Goldberg
[Abstract]

Neuroscience

Parallel Alzheimer's treatments suggest single therapeutic target

Alzheimer's disease is characterized by an accumulation of amyloid-β (Aβ) plaques on the brain that induce progressive memory loss. Studies related to Aβ metabolism and toxicity have yielded a wide range of potential drug targets for treating the disease. Lei Wang et al. used two independent research approaches-synaptic plasticity-based analysis and behavioral screening of synthetic compounds-to determine if some of these targets are better suited for drug development than others. The authors explored whether overlapping and converging effects would reveal single compounds that rescue Aβ-induced memory loss in both transgenic fruit fly and transgenic mouse models. According to the authors, two clinically available drugs and three synthetic compounds produced positive effects in behavioral tests and antagonized the Aβ oligomers-induced activation of epidermal growth factor receptor (EGFR), a signaling pathway that the authors subsequently linked to Alzheimer's dementia. These convergent results from parallel approaches, combined with trials with Aβ-induced deficits in transgenic animals, lead the authors to conclude that EGFR is a preferred target for treating Aβ-induced memory loss. According to the authors, the findings suggest that EGFR inhibition may represent an important therapeutic target for Alzheimer's disease in humans. — T.J.

"Epidermal growth factor receptor is a preferred target for treating Amyloid-βâ€“induced memory loss"
by Lei Wang, et al.
[Abstract]

Psychological and Cognitive Sciences

Exploring gender bias in academic science

Women remain underrepresented in many fields of academic science, despite increased efforts to recruit and retain women. Using a randomized, double-blind study design, Corinne Moss-Racusin et al. investigated whether academic science faculty exhibit gender biases that could contribute to this disparity. The authors asked a nationwide sample of 127 biology, chemistry, and physics professors to evaluate the application materials of an undergraduate student ostensibly applying for a lab manager position. All professors received identical applications, which were randomly attributed to either a male or a female student. The authors found that the male student was more likely to be hired and offered mentoring, was rated as more competent, and was offered a higher salary than the female student with the identical credentials. This bias was independent of the faculty member's gender, scientific discipline, age, and tenure status. Instead, the study revealed that the female student was less likely to be hired because she was viewed as less competent than the male student, according to the authors. Additional analyses revealed a preexisting subtle bias against women that undermined the faculty participants' perceptions and treatment of the female applicant. The findings suggest that the faculty members bias may be unintentional, stemming from widespread cultural stereotypes about women's competence in science, and could hinder female participation in science, the authors propose. – N.Z.

"Science faculty's subtle gender biases favor male students"
by Corinne A. Moss-Racusin, John F. Dovidio, Victoria L. Brescoll, Mark J. Graham, and Jo Handelsman
[Abstract] **OPEN ACCESS ARTICLE**

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