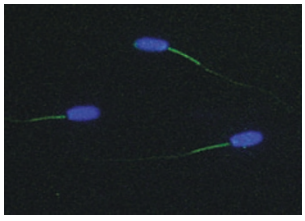
IN THIS ISSUE

COVER STORY

Natural-products chemists have unearthed a vast array of bioactive compounds through a classical approach including compound isolation and structure determination. However, the isolation of new chemical structures is a laborious method for finding a desired small-molecule needle in a metabolite haystack. In this issue, Challis and coworkers report the identification and structural characterization of a new natural product using a genome mining strategy. Their bioinformatics approach, which identified gene clusters involved in non-ribosomal peptide synthesis, led the authors to predict the existence of a previously unknown iron-binding siderophore in *Streptomyces coelicolor*. Using this insight, the authors isolated coelichelin from streptomyces culture under iron deficient conditions. Although their bioinformatics approach had predicted that the compound would be a tripeptide, their structural studies showed that coelichelin was a tetrapeptide. Further studies for detective work revealed that coelichelin is biosynthesized by three non-ribosomal peptide synthetase modules, which cooperate with a separate thioesterase domain. This nonclassical approach suggests that genome mining may offer an alternative route to the identification of new compounds of biological origin. **[Letters, p. 265; News & Views, p. 244]** *TLS*

Sperm vitality lift



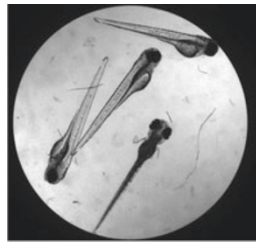
During artificial insemination, spermatozoa are vulnerable to oxidative damage, which reduces their functional lifesp=an and consequently affects fertility rates. Although the antioxidant vitamin E (α-tocopherol) can protect cells against oxidative damage, its intracellular delivery is hindered by its hydrophobicity. In this issue, Davis and coworkers report the effective intracellular delivery of α-tocopherol to porcine spermatozoa using a specialized hybrid polymer containing both targeting and antioxidant elements. They created a galactose-containing polymer that targets a galactose-binding protein on mammalian sperm cells. The visualization of sperm cell–polymer internalization by fluorescence showed that only galactose-containing polymers were internalized. Spermatozoa treated with the hybrid polymer had reduced oxidative damage, enhanced physiological properties and prolonged lifespan. Extensions of this work could provide a viable approach for enhancing mammalian fertilization during artificial insemination. **[Letters, p. 270; News & Views, p. 248]** *GW*

Nitrite as a signal

Although it is present in blood and organ tissue at high physiological levels, nitrite has been considered an inert by-product of nitric oxide oxidation, except when found at elevated concentrations. Recently a growing body of evidence has suggested that nitrite may have endogenous physiological functions, including vasodilation and protection from ischemic damage. Feelisch and colleagues now find that administration of nitrite to rats causes a dose-dependent increase in tissue nitrosation and nitrosylation. Multiple signaling pathways and molecules were regulated *in vivo* by nitrite, including cyclic GMP levels. Mechanistic evidence suggests that nitrite signals by a nitric oxide–independent pathway, but full elucidation of a chemical mechanism for direct nitrite modification of proteins will await future studies. Evidence for specific biochemical consequences of nitrite has implications for potential therapies and for human dietary guidelines. **[Articles, p. 290; News & Views, p. 245]** *JK*

In This Issue written by Greg Watt, Joanne Kotz and Terry L. Sheppard.

Seeing a beating heart



Small-molecule modulators of physiological parameters in whole organisms are valuable both as biological probes and as therapeutic leads. However, identifying small molecules with the desired *in vivo* phenotype can be a slow process. Burns and co-workers now report the first high-throughput assay for monitoring vertebrate organ function. Using zebrafish as a model system, the authors measured heart rate by automated fluorescence microscopy. This assay enabled the rapid characterization of heart rate changes induced by small molecules in living organisms and provides a new route to identifying drug leads for heart disease. [Brief Communications, p. 263] *JK*

Making neuronal contacts

Neuronal synapses are formed by a series of interactions between membrane proteins on presynaptic and postsynaptic neurons. The interaction between β-neurexin (Nrx) on the presynaptic neuron and neuroligin (Nlg) on the postsynaptic neuron is known to induce presynaptic differentiation. Isacoff, Groves and colleagues have developed an imaging technique for investigating the biophysical properties of the isolated Nrx-Nlg interaction. Using total internal reflection (TIRF) microscopy to follow the real-time interaction of Nlg in a planar lipid bilayer with Nrx-expressing cells, the authors found that Nlg rapidly co-localized with Nrx. The adhesive force of the Nrx-Nlg interaction was found to be relatively weak, suggesting that this interaction does not provide substantial neuronal adhesive force. A gradual incorporation of additional players into this model system can be expected to lead to a detailed physical understanding of neuronal synapse formation. **[Articles, p. 283]** *JK*

Mass spectrometry adds up

Mass spectrometry has become an enabling technology for chemical biologists by supporting the precise identification of biomolecules ranging from metabolites to macromolecules. Although mass spectroscopy traditionally has focused on the qualitative assignment of molecular structure, researchers have been looking for ways to use the technique to quantify the components of complex mixtures. In this issue, Ong and Mann review the applications of mass spectrometry and chemical labeling approaches to complex systems biology problems such as quantitative proteomic profiling. [Review Articles, p. 252] *TLS*