

## High-tech genetics

Forward genetic screens constitute a standard approach to study the function of genes in model organisms such as *Caenorhabditis elegans*. In two papers in this issue of *Nature Methods*, Hobert and colleagues apply new technologies to circumvent two critical bottlenecks in this process. First, they demonstrate that the COPAS Biosorter may be used for the automated isolation of *C. elegans* dopaminergic neuronal cell fate mutants. Second, they demonstrate the use of next-generation sequencing to pinpoint the single-nucleotide change responsible for an altered phenotype in mutant worms. Not only will these new strategies substantially reduce the time and labor involved in conducting screens, but they should also increase the scope and scale of forward genetics in the worm and possibly in other organisms in the future.

**Brief Communications p865 and p869,  
News and Views p863**

## Monitoring fast protein dynamics with TR-WAXS

Protein function is intimately related to dynamic motions, which can occur over a range of timescales. Optical spectroscopy methods have excellent time resolution but do not yield much information about what happens to the overall three-dimensional protein structure. Methods such as nuclear magnetic resonance (NMR) spectroscopy and time-resolved Laue crystallography offer the ability to monitor both dynamics and structure, but NMR spectroscopy is limited to slower time scales, and the need for well-ordered crystals can hinder relevant motions in Laue crystallography. Cammarata, Ihee and co-workers now describe developments to the synchrotron-based method of time-resolved wide-angle X-ray scattering (TR-WAXS) that now allows protein dynamics to be observed with nanosecond time resolution in solution, while also monitoring tertiary and quaternary conformational changes. They used TR-WAXS to gain insight into the kinetics and structural changes occurring during the rapid 'relaxed' to 'tense' transition in hemoglobin.

**Article p881**

## Spectral library building made simple

The typical method of identifying proteins using mass spectrometry technology is to compare the experimental peptide mass spectra to theoretical spectra derived by *in silico* digesting a protein sequence database. Although this has been the routine

for protein identification in the proteomics field, it is relatively sluggish, can be error-prone and is not feasible for organisms without sequence information. A better alternative would be to compare experimental spectra to a large database of well-validated, real peptide spectra, but such a reference spectral library is still a long way from being complete. In the meantime, Lam and coworkers offer an easy-to-use software toolkit to allow researchers to build spectral libraries from their own validated data or publicly available data. This toolkit, SpectraST, includes an algorithm for creating peptide consensus spectra as well as quality control filters for generating high-quality libraries.

**Brief Communication p873**

## Multiplex human genome resequencing

Next-generation sequencing is in principle well suited to the task of identifying human disease-associated polymorphisms by targeted resequencing in many individuals. However, the time and costs of such an endeavor are still high; one way in which efficiency could be improved is by resequencing in a multiplex format. Craig and colleagues use DNA bar codes to carry out simultaneous resequencing of genomes from multiple individuals with Illumina technology. By focusing on Encyclopedia of DNA Elements (ENCODE) regions in individuals previously genotyped as part of the HapMap project, they assessed the suitability of multiplex short-read sequencing for variant identification and genotyping in humans.

**Article p887**

## Harnessing Channelrhodopsin to study synaptic function

The neuromuscular junction of *Caenorhabditis elegans* is a popular model for the study of synaptic transmission.

Gottschalk and colleagues use Channelrhodopsin-2 (ChR2), a light-activated cation channel, to elicit photo-evoked synaptic transmission in the worm. The approach has several advantages over existing assays. Either cholinergic or GABA-ergic neurotransmission can be specifically photo-evoked, which is not possible with electrical stimulation, and repeated stimulation allows the study of synaptic plasticity without damage. Finally, rapid behavioral changes in response to photoactivation can be examined noninvasively, with the caveat that such effects are demonstrably complex and can in themselves give ambiguous results.

**Article p895**

