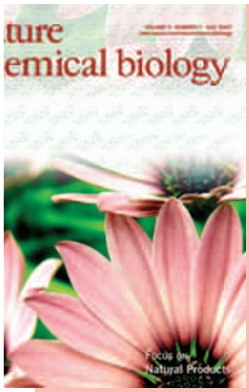


Focus on natural products

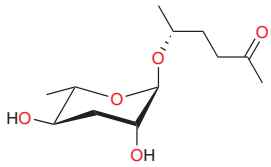
Natural products have long been appreciated for their structural diversity; they serve as privileged scaffolds in drug discovery efforts, and indeed a high percentage of currently existing drugs are natural products or derivations thereof. Although these compounds were initially defined as 'secondary metabolites' or 'cellular waste', continuing discoveries of new compounds and of their true biological roles have put this early definition to rest. This issue highlights these intriguing molecules, reporting on recent successes in and future goals of natural products research.

The road to many natural products remains a complex mystery. Fischbach and Clardy [**Commentary, p. 353**] suggest one reason for the intricacy of these pathways in a discussion about why enzymatic 'laziness' may be an evolutionarily favored feature of biosynthetic pathways. To bypass the complexity of these enzymatic pathways altogether, Maimone and Baran [**Review, p. 396**] discuss organic chemists' success in the total synthesis of several terpenes, which has not only allowed access to some daunting molecules but has also pushed the field of synthetic chemistry forward. Roberts [**Perspective, p. 387**], on the other hand, points out that elucidating biochemical pathways offers the opportunity to more intelligently collect compounds from a cellular host, and also to use metabolic engineering to optimize production of the desired compound. Also within the theme of biosynthesis, we feature a recent report on the structure and mechanism of a cofactor-independent oxidase that catalyzes an important step in the biosynthesis of vancomycin [**News & Views, p. 374**], and we highlight a mechanistic investigation of a flavin-dependent IPP isomerase that is involved in isoprenoid biosynthesis [**Research Highlights, p. 377**].

In addition to ongoing efforts to determine structure and biosynthetic routes, inquiries into the physiological roles of these compounds have gained momentum. Gershenzon and Dudareva [**Review, p. 408**] look further at these compounds and mixtures, examining biological communication, primarily between plants and insects, with natural products as the language. Similarly, scientists at the Hans Knöll Institute [**Elements, p. 367**] are learning not only how, when and why natural products are biosynthesized, but also what they mean in interspecies communication. We also highlight two studies that probe the roles and recycling of natural products in the cell [**Research Highlights, p. 377**].

Beyond deciphering the functions of natural products, scientists have coopted known biosynthetic pathways to create completely new products. Wilkinson and Micklefield [**Perspective, p. 379**] examine some recent successes and current challenges in the field of combinatorial biosynthesis. In another incarnation of coopting biosynthesis, Strobel and Strobel [**Commentary, p. 356**] describe a new training program in which undergraduates get a taste of scientific discovery by studying endophytes and their natural products. Finally, to return to the historical strength of natural products, developing a quantitative understanding of how natural product mixtures can be successful as drugs remains a challenge; Schmidt *et al.* [**Commentary, p. 360**] make the case for improved testing to provide confidence in botanical therapeutics. In any case, we have confidence that natural products will continue to furnish interesting scientific questions in the years to come. *CG*

Would the real dauer pheromone please stand up?

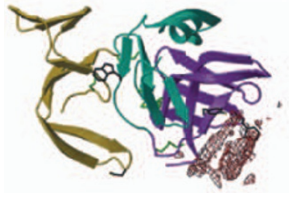


The nematode *Caenorhabditis elegans* can survive starvation and other harsh conditions by entering a dauer phase. It is thought that a dauer pheromone or a mixture of pheromones serves as a signal for groups of worms to enter this nonfeeding larval stage. Previously, a single ascaroside, a carbohydrate derivative, had been identified as the dauer pheromone. Butcher *et al.* suspected that both its poor yield from dauer-inducing extracts and the need for high concentrations for activity indicated that it wasn't the only compound involved. From a three-step purification process, the authors found two ascaroside compounds that were substantially more potent at promoting dauer than the original one. The new compounds account for nearly all of the biological activity attributed to the natural pheromone in traditional bioassays, and they should prove useful in elucidating the mechanisms of dauer formation and the behavior of the worms in their natural soil environment. [Letters, p. 420; News & Views, p. 368] *MB*

Calcium detection in a FlAsH

Intracellular calcium regulates many biological processes, but some aspects of ion movement through calcium channels remain a mystery. Current methods for visualizing calcium influx are limited by inappropriate kinetics of Ca^{2+} binding or the large size of fused protein sensors. Tour *et al.* now report a new reagent for monitoring calcium: Calcium Green FlAsH, which binds to modified channels through a tetracysteine-binding arsenic motif. The reagent successfully detects channel opening in response to cellular injury. By comparing the signal of the reagent with that generated by GFP–tagged channels, the authors made the surprising discovery that only a small percentage of calcium channels are active in this response. [**Articles, p. 423; News & Views, p. 369**] *CG*

Towards immortalizing flies



Methuselah (Mth) is a member of the class B G protein–coupled receptors (GPCRs), which have large extracellular domains (ectodomains) that can recognize their cognate ligands independently of the adjacent protein core of seven transmembrane spans. As its name implies, mutations that downregulate *mth* increase the life span of *Drosophila melanogaster*. To identify new high-affinity ligands that bind the ectodomain of Mth, Ja *et al.* screened an mRNA display library and found several active peptides, all of which contained a conserved RWR motif and caused increased longevity when expressed *in vivo*. From the crystal structure of the Mth ectodomain with an RWR motif peptide, the authors concluded that the peptide binds at an interface between the ectodomain and the extracellular loops. Given that GPCRs are common targets of pharmaceuticals, understanding the mode of interaction of active Mth ligands should prove useful for designing compounds that affect the aging process. [**Letters, p. 415; News & Views, p. 371**] *MB*

In This Issue written by Mirella Bucci and Catherine Goodman