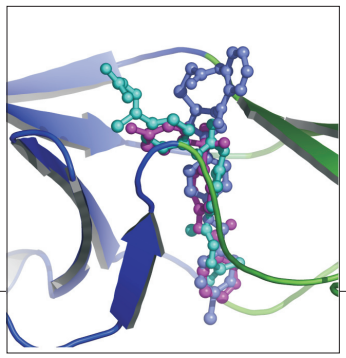


In this ISSUE

acs chemical biology

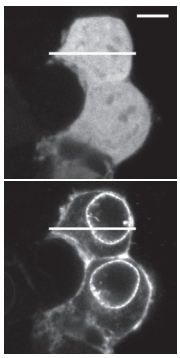
Computing the Way to New Antivirals

Dengue viruses, mosquito-borne human pathogens responsible for causing dengue fever and related diseases, infected nearly 100 million people and caused >20,000 deaths in 2007. Treatment strategies against dengue viruses are alarmingly scarce, with no vaccine or antiviral drugs available to date. Zhou *et al.* (p 765) elegantly blend computational and experimental methods in their search for antiviral compounds against dengue viruses.

Straying from the more traditional approach of targeting a viral enzyme, the authors aimed to find inhibitors of the viral E protein, a structural glycosylated envelope protein involved in virus maturation and host-cell entry. Computational high-throughput screening was used to search through 142,000 small molecules with potential to bind the E protein. Of these, the 23 most promising were evaluated in cellular assays and NMR binding studies, leading to the identification of an exciting lead compound.

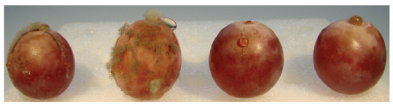
Protein–Protein Interactions Take the Bait

Protein–protein interactions play fundamental roles in cellular processes, and the discovery of and insight into these interactions are crucial for furthering our understanding of biological events and for developing new therapeutics against a wide variety of diseases. Piljić and Schultz (p 749) now present an innovative protein translocation-based approach that enables exploration of protein–protein interactions in live cells.



The approach exploits the protein annexin 4, which translocates from the cytoplasm and nucleoplasm to the plasma and nuclear membranes, respectively, in response to an increase in intracellular calcium levels. With the help of appropriate fluorescent tags and the fusion of a "bait" protein, such as one component of a multiprotein complex, to annexin 4, the translocation of proteins that interact with the bait protein can be easily monitored. This method is an exciting addition to the toolbox of techniques used to examine protein–protein interactions.

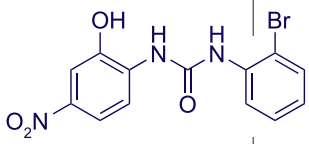
Clearing a Gray Area of Gray Mold



Botrytis cinerea, also referred to as gray mold, is a fungal pathogen that affects hundreds of plant species, although notably *B. cinerea* infection of Sémillon grapes also happens to be instrumental in the production of certain dessert wines. The fungus secretes many nonspecific phytotoxins including the bicyclic sesquiterpene botrydial, but the biosynthetic pathways responsible for many of these compounds are just beginning to be deciphered. To this end, Pinedo *et al.* (p 791) report the characterization of the botrydial biosynthetic gene cluster.

Building on knowledge gained from the previously identified *BcBOT1* gene and recent sequencing of the *B. cinerea* genome, quantitative reverse-transcription polymerase chain reaction analysis facilitated identification of four additional genes involved in botrydial biosynthesis, *BcBOT2–5*. Detailed characterization of *BcBOT2* revealed that it encodes a sesquiterpene synthase, the first of its kind obtained from any fungal or plant source.

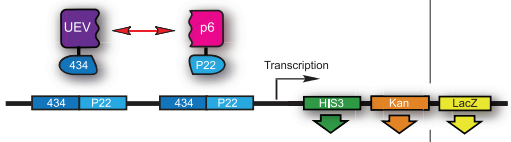
Inflaming the Fight Against Alzheimer's



Alzheimer's disease (AD) is a devastating, incurable neurodegenerative disorder affecting nearly 5 million people in the U.S. alone. Though not fully understood, the cause of AD is linked to aberrant processing of the amyloid precursor protein (APP), which leads to aggregation and accumulation in the brain of the neurotoxic peptide β-amyloid (Aβ). Interestingly, up-regulation of certain inflammatory chemokines and chemokine receptors has been associated with altered APP processing, but it is unclear whether this up-regulation is a cause or effect of AD progression. Bakshi *et al.* (p 777) now present compelling evidence that increased expression of the chemokine receptor CXCR2 drives Aβ production.

Screening of a focused library of chemokine ligands led to the identification of a small-molecule CXCR2 antagonist that selectively inhibits Aβ production in cells and in mouse models of AD. These findings offer important insight into the role of chemokines in AD and provide potential new targets and lead compounds with which to help tackle the disease.

Putting a Gag on Gag



The remarkable yet exasperating ability of HIV to mutate and become resistant to the very drugs designed to destroy it illustrates the desperate need for novel anti-HIV therapeutic strategies. Notably, specific interactions between host and viral proteins may be inherently less susceptible to viral mutation. Taking this line of attack, Tavassoli *et al.* (p 757 and Point of View p 745) identify a cyclic peptide capable of disrupting the interaction between the HIV Gag protein and the host protein TSG101.

The Gag–TSG101 interaction is essential for the effective release of viral particles from virus-infected cells. When tagged with a membrane translocation-promoting sequence, a cyclic peptide specifically inhibited the production of virus-like particles in cultured human cells.

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