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In This Issue

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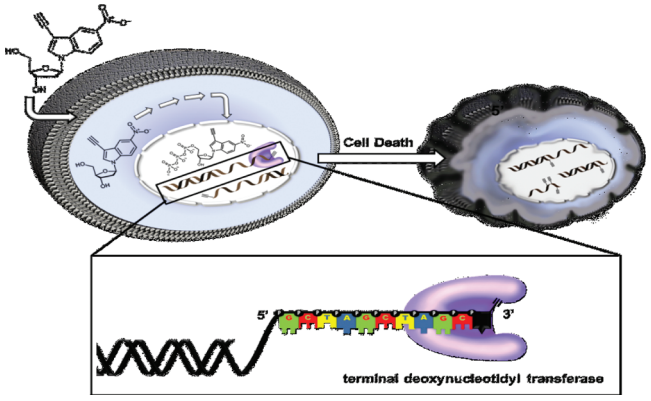
AN ALL IN ONE AGENT FOR ALL

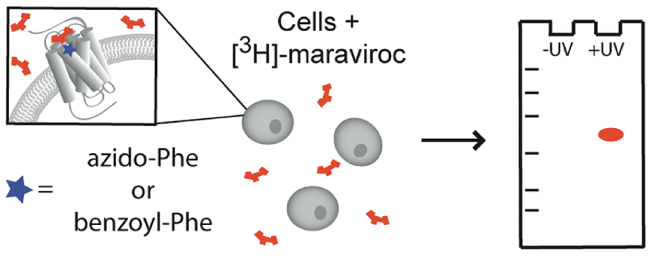
Terminal deoxynucleotidyl transferase (TdT) is a unique DNA polymerase in that it adds individual nucleotides to existing DNA strands without use of a template strand to guide the sequence of the newly generated strand. This unusual aspect to its mechanism contributes to its important role in development of the immune system, but TdT is also implicated in acute lymphocytic leukemia (ALL), the most common type of cancer in children. Motea *et al.* (DOI: 10.1021/cb300038f) now report the identification of a non-natural nucleoside with both diagnostic and therapeutic potential for ALL.



The nitro-indolyl-containing nucleoside was shown to selectively halt the growth of and kill ALL cells that overexpress TdT, demonstrating its potential as an anti-leukemia agent. In addition, the strategic positioning of a triple bond in the molecule enabled its conversion to a fluorescent compound after its incorporation into DNA, endowing it with diagnostic capabilities. This unique combination of attributes could facilitate the clinical development and applications of this and similarly designed compounds.

ILLUMINATING GPCR BINDING SITES

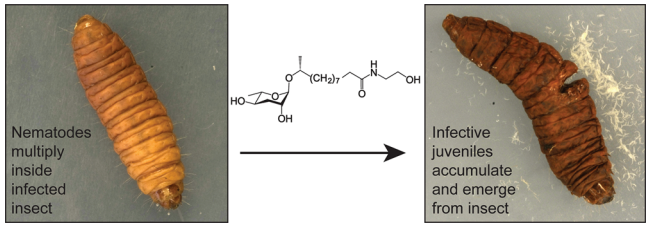
The majority of best-selling drugs, including treatments for schizophrenia, allergies, and ulcers, target a family of transmembrane signaling proteins called G protein-coupled receptors (GPCRs). However, rational drug design targeting GPCRs has been hindered by challenges in gaining structural information for the proteins, especially in complex with inhibitors. Grunbeck *et al.* (DOI: 10.1021/cb300059z) now report an innovative method based on photo-cross-linking for identify the binding site of small molecule GPCR inhibitors.



Using the interaction between the HIV drug maraviroc and CC chemokine receptor 5 (CCR5), a GPCR required for HIV infection, as a model system, the authors developed a photo-cross-linking technique in which unnatural photo-cross-linker amino acids were strategically placed in CCR5. Cells expressing the mutant protein were incubated with radiolabeled maraviroc and exposed to ultraviolet light. Using this strategy, the authors showed that maraviroc binds within the transmembrane bundle of CCR5 and also validated a molecular model of the interaction. This method should be generally applicable to any receptor–ligand interaction in which the protein can be expressed in cell culture and the ligand can be radiolabeled.

SIGNALING TO JUVENILE WORMS

Entomopathogenic nematodes are parasites that infect soil insects, such as the larvae of butterflies and beetles, and adult crickets and grasshoppers. While in a developmental stage called infective juveniles, the nematodes infect their prey and then mount a second attack from the inside by regurgitating bacteria they store in their gut. During their cohabitation with the nematodes in the insect, the bacteria direct further development of the infective juveniles by secreting small signaling molecules. However, the structures of these pheromones have remained elusive. Now, Noguez *et al.* (DOI: 10.1021/cb300056q) report the identification of one such pheromone that prevents the development of infective juveniles.



Using activity-based assays and nuclear magnetic resonance-based structural characterization, the pheromone was determined to be a member of the ascaroside family of glycolipids. Notably, related ascarosides that regulate development of other nematodes had minimal activity in the entomopathogenic nematode. This insight into chemical signaling in parasitic nematodes will facilitate development of molecular tools to probe and manipulate their activity.

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