November 6, 2012 | vol. 109 | no. 45 | 18235–18626

In This Issue

PNAS
Proceedings of the National Academy of Sciences of the United States of America
www.pnas.org

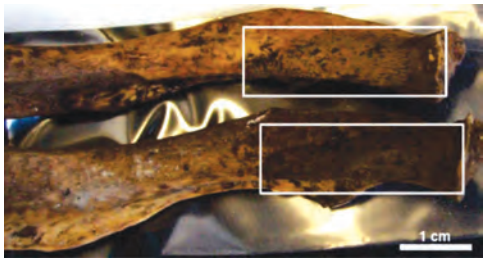
Contributions of gasoline and diesel vehicles to air pollution

Unburned hydrocarbons emitted from gasoline and diesel vehicles contribute to the formation of secondary organic aerosol (SOA), tiny particles that can harm human health, reduce visibility, and impact climate. But the relative importance of gasoline and diesel sources for SOA formation remains unclear. Drew Gentner et al. (pp. 18318–18323) characterized and quantified the hydrocarbons present in samples of gasoline and diesel fuel from California, and determined the SOA formation potential of diesel exhaust, gasoline exhaust, and nontailpipe gasoline emissions. The authors then used this information to estimate the relative contributions of each hydrocarbon source to reactive gas-phase organic carbon in the ambient air in Bakersfield, CA, and in a roadway tunnel in Oakland, CA. The authors found that diesel exhaust forms 15 times more SOA than gasoline per liter of fuel burned, and estimate that diesel exhaust is responsible for 65–90% of a region's vehicular-derived SOA, depending on the relative amounts of gasoline and diesel used. The authors suggest that characterizing the chemical composition of liquid fuels and fuel-derived compounds in the ambient atmosphere could provide insights into SOA formation from motor vehicles, and may lead to improved pollution control policies, fuel regulations, and methodologies for future studies on SOA. — N.Z.

Vehicles at the entrance of the Caldecott Tunnel in Oakland, CA.

Genotype of an ancient variety of *Mycobacterium tuberculosis*

Mycobacterium tuberculosis is the second deadliest infectious agent worldwide, yet little is known about the bacterium's historic genetic variations and how such historic strains have evolved over time. Using a next generation sequencing approach, Abigail Bouwman et al. (pp. 18511–18516) obtained the detailed genotype of a historic strain of *M. tuberculosis* from a female adolescent buried sometime between 1840 and 1911 in a crypt in Leeds, England. The authors extracted DNA from a rib bone that displayed signs of a possible pulmonary tuberculosis infection, and used hybridization capture to generate a sequencing library comprised of 260 target regions of the *M. tuberculosis* genome. Sequencing analysis of the captured DNA fragments confirmed the presence of *M. tuberculosis*. In addition, the authors successfully genotyped 218 single nucleotide polymorphisms and eight insertions or deletions. A comparison of the historic strain's sequences with the equivalent regions of 17 completely sequenced modern strains revealed that the ancient strain belongs to a lineage that is uncommon today, but was known to have been present in North America during the early 20th century. The authors suggest that genotyping historic strains of *M. tuberculosis* could enable comparisons between strains from different geographic locations and time periods, and may yield clues about the pathogen's evolutionary history. — N.Z.

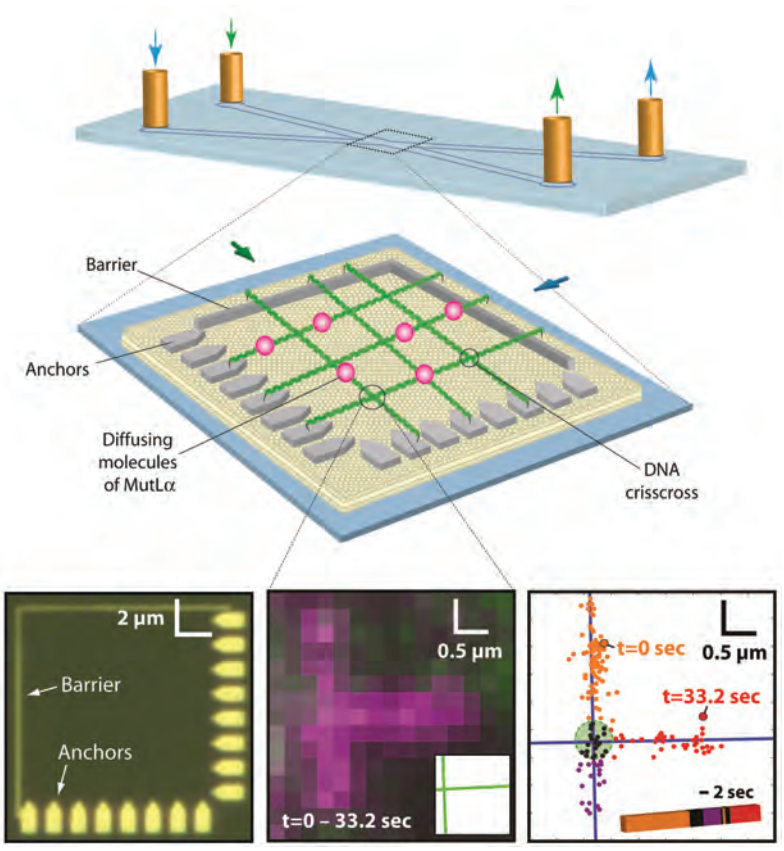


Rib bones, with signs of possible pulmonary tuberculosis infection (boxed areas), from a female buried sometime between 1840 and 1911 in Leeds, England.

www.pnas.org/cgi/doi/10.1073/iti4512109

How DNA mismatch repair proteins find their targets

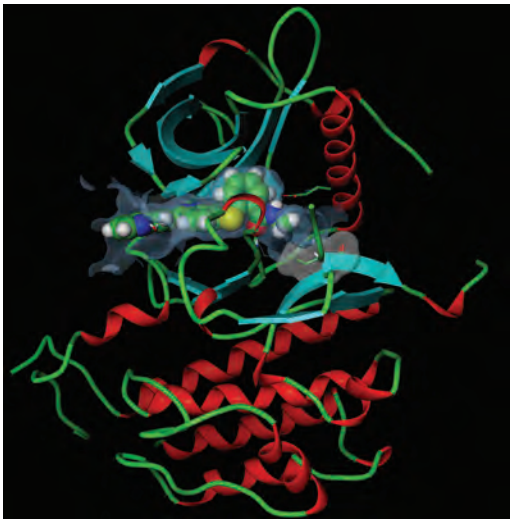
Proteins have the ability to locate specific targets on DNA, but how they do so remains poorly understood. Jason Gorman et al. (pp. 18251–18252) used single-molecule microscopy to visualize the postreplicative mismatch repair (MMR) proteins MutSα and MutLα, which correct errors in DNA synthesis, as they search for their DNA targets. The researchers used total internal reflection fluorescence microscopy (TIRFM) and nanofabricated DNA curtains—DNA strands anchored to a lipid bilayer—containing mismatches to observe as MutSα searched for DNA mismatches and MutLα found the mismatch-bound MutSα. The researchers found that MutSα can find mismatched bases either through 1D sliding over the DNA, or 3D diffusion. MutLα located the mismatch-bound MutSα either by 1D hopping over stretches of DNA or by 3D transfer between juxtaposed DNA segments. The mismatch-bound MutSα/MutLα complex was released upon ATP-binding, and scanned the flanking DNA by 1D-diffusion. The researchers also found that upon release from a mismatch, MutSα is altered so that it no longer targets mismatches, preventing it from binding again to the same site of DNA damage. The study provides a direct visualization of how MMR proteins use different modes of diffusion to recognize and repair damaged DNA, according to the authors. — S.R.



DNA curtains allow visualization of protein transfer.

VEGFR TK inhibitor efficacy depends on conformational differences

Anticancer drugs known as tyrosine kinase (TK) inhibitors block critical TK activity and disrupt vascular endothelial growth factor receptor (VEGFR) signaling. Four structurally diverse VEGFR TK inhibitors have been approved to treat renal cell carcinoma, a cancer that has been linked to aberrant VEGF signaling; however, the therapies' distinct clinical efficacies and VEGF-related safety profiles suggest that each inhibits its shared molecular target differently. In their Feature Article, Michele McTigue et al. (pp. 18281–18289) determined the potencies, time-dependence, selectivities, and X-ray structures of drug–kinase complexes for the VEGFR TK inhibitor class and found unique drug–kinase interactions that correspond to differences in potency and ligand efficiency. According to the authors, distinct conformations of the juxtamembrane region, a key VEGFR TK regulatory domain, fundamentally underlie the performance differences. In addition, the authors determined that the identified drug–kinase structural interactions explain trends in in vitro measurements that translate well to clinical performance. The findings, which result from a detailed, side-by-side comparison of molecular interactions within a single drug class, demonstrate a principle that can be used to optimize the in vivo performance of future therapies, according to the authors. — T.J.



Crystal structure of VEGF receptor tyrosine kinase.