X-rays reveal how soil bacteria carry out surprising chemistry

Researchers from Singapore, Japan, the UK and USA have discovered how soil bacteria carry out surprising chemistry, defying a longstanding set of chemical rules and thus paving the way for new synthesis of polyether drugs.

Principal investigator, Chu-Young Kim, Assistant Professor at the Department of Biological Sciences of the National University of Singapore (NUS) Faculty of Science, and his group have made use of powerful X-rays to decipher how antibiotic-producing bacteria defy a longstanding set of chemical rules.

Their result, reported today in Nature, details how a soil bacterium, Streptomyces lasaliensis, is able to convert an epoxide into a six-membered cyclic ether during synthesis of lasalocid, a natural polyether antibiotic. The fact that bacteria can perform such chemistry has puzzled chemists and biologists for decades because this type of chemical transformation is known to be kinetically unfavorable.

According to "Baldwin’s Rules for Ring Closure," which govern the way these rings form, lasalocid should contain a five-membered ring instead of the observed six-membered ring.

“Our study has broad implications because the six-membered cyclic ether is a common structural feature found in hundreds of drug molecules produced by nature," said Dr Kim. "We have analysed the genes of six other organisms that produce similar polyether drugs and we are now confident that the biosynthetic strategy we have uncovered is also used by those organisms.”

The solution to the molecular mystery depended in large part on a deeper understanding of the unique enzyme Lsd19 that catalyses the formation of two cyclic ether moieties that are part of the lasalocid structure. To determine the protein's atomic structure, researchers hit frozen crystals of Lsd19 with X-rays at the Stanford Synchrotron Radiation Lightsource, SLAC National Accelerator Laboratory, and analysed how the crystals diffracted the X-rays. "You need atomic-level detail of the protein's structure to understand what's really happening," said co-author Irimpan Mathews, a staff scientist at SLAC.

Lessons from the bugs

"The bugs have taught us a valuable chemistry lesson," Dr Kim said.

"With a new understanding of how nature synthesises the six-membered rings, chemists may be able to develop new methods to produce polyether drugs with ease in the laboratory. Alternatively, protein engineers may be able to use our results to develop a biofactory, where polyether drugs are mass produced using fermentation. Either method will make more effective and more affordable drugs available to the public.”

Next challenge: Elucidating how nature synthesises an anti-cancer compound

Dr Kim's group has moved on to their next challenge: investigating how nature synthesises echinomycin, an anti-cancer compound produced, again, by soil bacteria. "We still have much chemistry to learn from the bugs."

Additional authors included Kinya Hotta, Xi Chen, Hao Li and Kunchithapadam Swaminathan of the National University of Singapore, Robert S. Paton of Oxford University, Atsushi Minami and Hideaki Oikawa of Hokkaido University, Kenji Watanabe of the University of Shizuoka and Kendall N. Houk of the University of California at Los Angeles.

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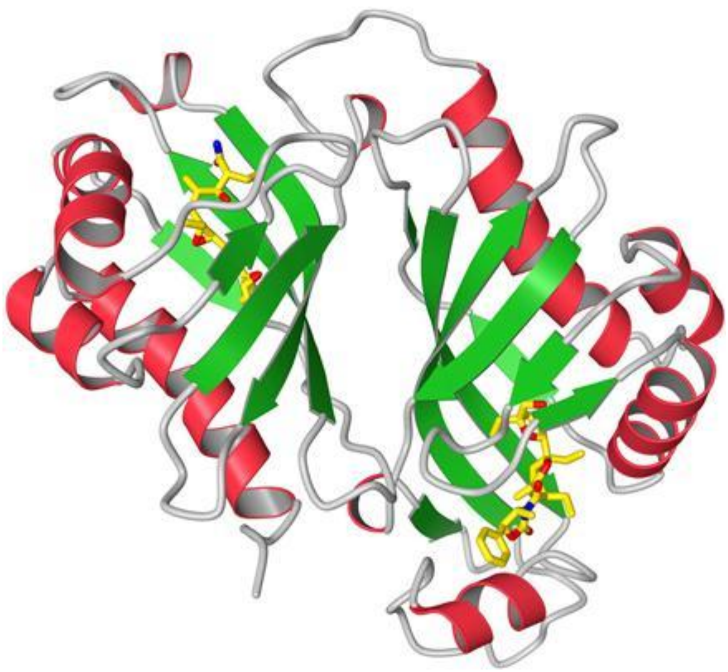
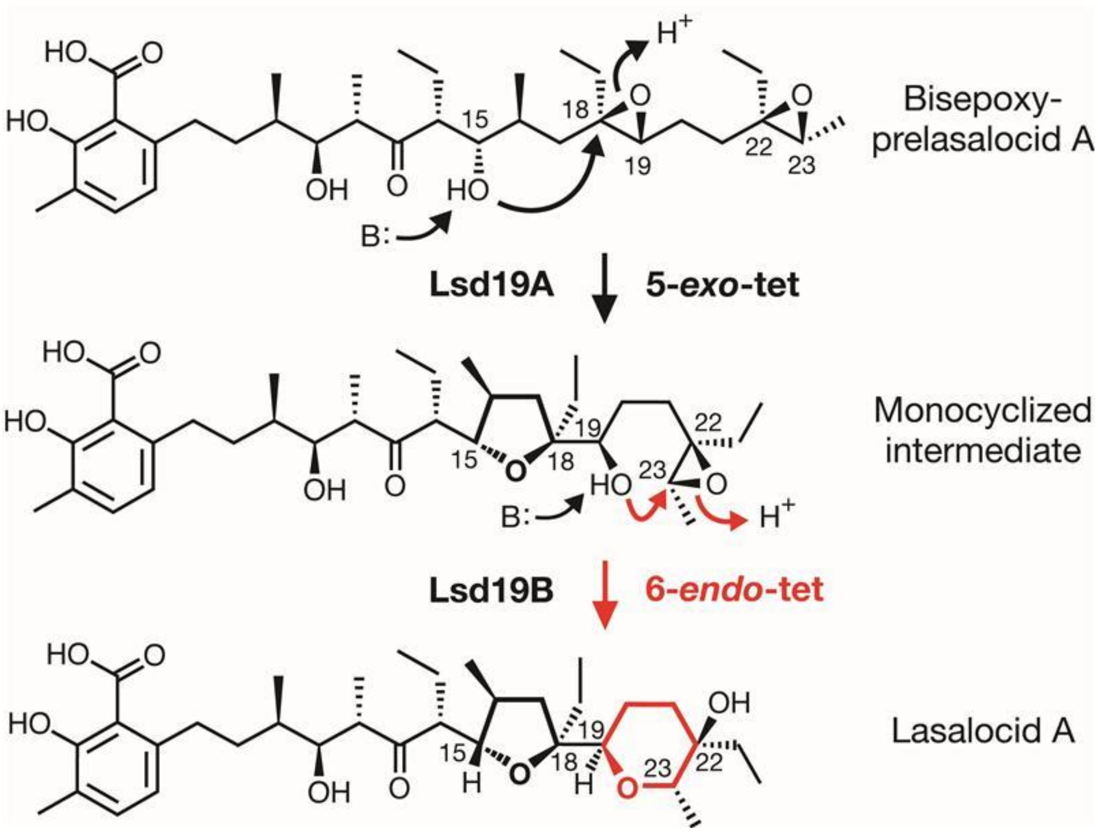


The crystal structure of Lsd19 determined at 1.59 Å resolution (PDB ID: 3RGA). The X-ray diffraction data was collected at beam line 7-1 of Stanford Synchrotron Radiation Lightsource. (Credit: Dr. Kinya Hotta)



Epoxide-opening cyclic ether formation catalysed by Lsd19. The disfavored 6-endo-tet reaction is highlighted in red. (Credit: Dr. Kinya Hotta)