對外合作組織與機構
動態報導

2017/9/1

"MONKEY WRENCH" MOLECULE JAMS TUBERCULOSIS PROTEIN

阿岡實驗室開發一阻抗性分子，可阻礙結核桿菌之蛋白質生成

By Savannah Mitchem •August 4, 2017

Tuberculosis has now surpassed HIV worldwide as the leading cause of death due to infectious disease. The bacteria that causes this disease, *Mycobacterium tuberculosis* (Mtb), is quickly developing resistance to currently available antibiotics, increasing the urgency for discovery of new drugs.

Scientists at the U.S. Department of

報告摘要(KEY INFORMATION)

1. 結核病在全球各地廣泛流行，已超越愛滋病成為感染性疾病致死的主因。結核病的病原菌 Mycobacterium tuberculosis（結核桿菌），對於現行使用的抗生素已經快速發展出抗藥性，這使得新藥的開發更為緊迫。
2. 七月初，混和阿摩尼亞的燃料在日本關西一座燃煤發電廠進行測試。阿摩尼亞和氫一樣，其燃燒不會產生二氧化碳，因此近年來作為一種低碳電力燃料已備受矚目。
3. 在英國，空污問題每年對 4 萬人造成嚴重影響，採取因應手段已是十分迫切。7 月 26 日，英國環境秘書長 Michael Gove 宣布將自西元 2040 年起禁止汽油車及柴油車的銷售。該政策可能作為一對抗污染的基本政策，將機動車輛對石油、柴油的依賴轉向電力、油電混合或其他低污染排放之能源。
4. 當月亮擋住太陽、發生日蝕現象的時候，我們可以看見月亮的邊緣。史丹佛的研究團隊運用這樣的概念，以經過精確計算位置與角度之人造衛星遮蔽恆星、使所謂「人工日蝕」發生，再以另一人造衛星進行觀測，以期找到存在生命的他方行星。
5. 一工程師團隊正指望能從人群中找到答案。藉由模擬人體運動的情形，可使我們對神經系統如何調控骨骼、肌肉的過程認識更深，期待終有一天能帶給腦性麻痺孩童更好的生活。

Energy's (DOE) Argonne National Laboratory were part of a recent discovery of a new molecule called an inhibitor that attacks tuberculosis-causing bacteria by cutting off its production of a chemical necessary for its survival.

Creating antibiotics involves developing inhibitors that can effectively block essential bacterial processes. Equally important is to keep finding novel pathways to target so that when the bacteria eventually adapt to resist one antibiotic, there are still other avenues available to exploit.

The new study, a collaboration between Argonne, the University of Chicago and the Broad Institute of Harvard and MIT, identified an inhibitor that works by blocking the action of an important protein in Mtb. The inhibitor binds to a channel within the protein that connects its two parts, killing the bacteria through an ironic twist. The inhibitor forces one part of the protein to produce the components necessary to create an essential chemical, tryptophan, while at the same time reshaping the channel to intercept those ingredients before the other part of the protein can use them.

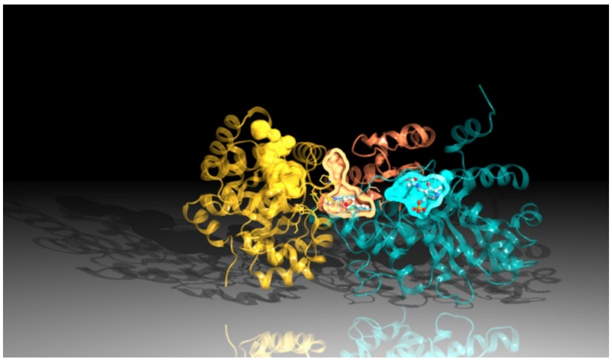
These types of inhibitors, called allosteric inhibitors, do not bind to the part of the protein actually responsible for producing the target chemical. Instead, they act as a monkey wrench jammed into other less obvious parts of the complicated machinery of the bacteria. The inhibitor identified in this research, described in a recent paper in *Nature Chemical Biology*, is now one of the most deeply studied allosteric inhibitors to date.

The targeted chemical, tryptophan, is a substance that is crucial in giving all living cells their structure and protecting them from their surroundings. Human cells have to rummage tryptophan from food or bacteria in the gut, but Mtb cells can manufacture their own tryptophan using a complex protein called tryptophan synthase. "We knew that one way of killing these bacteria was finding a way to block the tryptophan synthase," said Karolina Michalska, an Argonne crystallographer and author of the study.

Before the collaboration began, a group of scientists at the Broad Institute put a small amount of the bacteria in petri dishes and placed different potential inhibitors in each one. Out of a library of over 80,000 tested potential inhibitors, only a few killed the Mtb. The scientists suspected that one of these inhibitors shut down the Mtb's tryptophan synthase, but they needed to see what was happening on the molecular level.

Argonne scientists heard about the work at the Broad Institute, and the two groups began to collaborate. Argonne produced tryptophan synthase for the Broad Institute to use for testing the inhibitor. They also determined the structure of the synthase with the inhibitor bound to it by exposing crystals composed of the protein-inhibitor complex to high-energy X-rays from Argonne's Advanced Photon Source (APS) and recording how the electrons in the molecule scattered the light.

"The collaboration made it possible for us to determine the allosteric nature of the inhibitor and the nuances of how the inhibition worked," said Deborah Hung, a professor at the Harvard Medical School and co-director of the Infectious Disease and Microbiome Program at the Broad Institute.



The structural analysis determined that there are two key parts that make up tryptophan synthase. When one of the regions signals to the other that it is ready, the other region makes a chemical substance called indole. The indole then travels through a channel to the other region of the tryptophan synthase where it combines with another substance to create the final product, tryptophan.

A slight instability in the channel would allow the indole to travel to the other side, but the inhibitor is shaped so that it stabilizes the channel, preventing the indole from moving. Since the indole can't reach the far side of the protein, the inhibitor blocks the production of tryptophan.

"It actually works in quite a sneaky way," said Andrzej Joachimiak, Director of Argonne's Structural Biology Center and the Midwest Center for Structural Genomics. "The inhibitor both forces the tryptophan synthase to produce the indole and prevents it from carrying out its ultimate duty."

Although researchers are optimistic about this inhibitor's potential as an antibiotic, it is still far from being an available pharmaceutical. They have studied how human tissue would react to the molecule and have confirmed that it is non-toxic, but experiments in mice have shown that the inhibitor would be metabolized by the body too quickly. Research is now being done to refine the structure of the inhibitor so it persists in the bloodstream for an extended period of time.

The research was funded by the National Institutes of Health, the Broad Institute Tuberculosis Donor Group, the Pershing Square Foundation and the Bill and Melinda Gates Foundation. Work done at the APS, a DOE Office of Science User Facility, was supported by DOE's Office of Science.

An article based on the study, "A small-molecule allosteric inhibitor of *Mycobacterium tuberculosis* tryptophan synthase," was published in the July 3 issue of *Nature Chemical Biology*. Argonne researchers in the study included Joachimiak, Michalska, Robert Jedrzejczak and Natalia Maltseva. Researchers from MIT, Harvard, the Massachusetts General Hospital, Northwestern University and the University of Chicago also participated in the study.

DEVELOPMENTS IN PROMOTING THE USE OF AMMONIA
推行阿摩尼亞運用之進展

Yoshiaki Shibata

In early July, a test for mixed combustion of ammonia was conducted in Chugoku Electric's coal thermal power plant. Like hydrogen, ammonia, which does not produce CO2 when burned, has been receiving attention as a low-carbon electricity fuel in recent years.

Currently, ammonia is used primarily as a fertilizer and chemical material, but there have been attempts in the past to use it for energy. Records show that ammonia was used during the two World Wars as a fuel for buses and cars in Europe to deal with the unstable supply of petroleum products. Further, around 1960, it was used as rocket fuel for a US high-altitude, supersonic prototype. After that, ammonia was studied as an energy carrier for transporting and storing hydrogen rather than as an energy source itself. The potential of ammonia as an energy carrier was explored under the International Clean Energy Network Using Hydrogen Conversion (WE-NET) in Japan and in the DOE's office of hydrogen energy in the US in 2006.

In Japan, the use of ammonia has been driven in recent years by the Cross-ministerial Strategic Innovation Promotion Program (SIP) launched in FY2014 under the Council for Science, Technology and Innovation. The Program aims to use ammonia as a fuel as well as an energy carrier, and promotes R&D on the ammonia direct-combustion gas turbine and ammonia fuel cell as well as on mixed combustion in coal thermal power plants described above. The underlying idea is that it is more efficient to use ammonia directly as a fuel rather than decomposing it and using the hydrogen obtained, as is done when using ammonia as an energy carrier. As the SIP is scheduled to end in FY2018, the Green Ammonia Consortium of 21 major institutes and corporations is due to be launched soon to continue the research and development.

Ammonia has various advantages in addition to not emitting CO2 when used. For instance, it has an established production technology (the Haber-Bosch process) and is available in large quantities worldwide as a fertilizer. The availability of established technology and supply chains means that there are relatively few barriers to overcome in each phase of RDD&D (research and development, demonstration and deployment). However, ammonia is a deleterious substance that requires strict security control, which makes it unsuitable for distributed use and more suited for large-scale thermal power generation under centralized management. Further, ammonia must be produced without CO2 emissions. As the hydrogen required for ammonia synthesis is currently produced from natural gas, CCS is essential for CO2-free ammonia production. Alternatively, hydrogen would have to be produced from renewable energies.

For energy carriers, studies on a technologically-feasible and economically-efficient supply chain are required. Attention must be paid to the developments in R&D for ammonia, alongside liquefied hydrogen and methylcyclohexane on which demonstrations are separately underway.

MOVES TOWARD GASOLINE/DIESEL VEHICLE BAN IN EUROPE AND ITS IMPACT

歐洲的汽油及柴油禁令

Ken Koyama

On July 26, British Environment Secretary Michael Gove announced that a ban would be imposed on sales of new gasoline and diesel vehicles from 2040. As air pollution has been estimated to have seriously affected 40,000 people in Britain annualy, measures against air pollution have been viewed as urgent. The ban on gasoline and diesel vehicles might have been announced as a fundamental anti-pollution policy to switch from gasoline and diesel vehicles to electric, hybrid and other clean vehicles emitting no or less pollutants.

The switch from gasoline and diesel vehicles is expected to contribute not only to easing air pollution but also to reducing carbon dioxide emissions and play a key role in Britain's global warming and climate change policy. As Britain and other participants in the Paris Climate Agreement are set to voluntarily reduce greenhouse gas emissions and enhance the reduction in the future under the Agreement that has taken effect, the British measure to ban gasoline/diesel vehicles is expected to hold a key position.

In fact, a similar policy was announced in France on July 6 prior to the British announcement. French Ecology Minister Nicolas Hulot then said France will ban sales of gasoline and diesel vehicles by 2040 to reduce CO2 emissions. The announcement came just before a Group of 20 Summit in Germany, indicating that France would like to take leadership in climate change measures as the host of the 21st Conference of Parties to the United Nations Framework Agreement on Climate Change that achieved the Paris Agreement.

Britain and France, ranked just after Germany as the largest European vehicle country, have thus come up with the gasoline and diesel vehicle sales ban starting in 2040. In addition to Britain and France, the Netherlands and Norway are moving to ban gasoline and diesel vehicles. Even in Germany, the federal legislature adopted a non-binding resolution calling for a similar ban in October 2016. Apart from the national level, Swedish vehicle manufacturer Volvo as a symbolic move, has offered to sell only electric vehicles from 2019. Other automakers have also offered strategies to switch to electric and other clean vehicles.

The situation is complicated in Germany that has a giant auto industry. On August 2, German automakers including Volkswagen and Daimler announced to recall a total of 5.3 million diesel vehicles to enhance reduction of emissions. The improvement of diesel vehicles' environmental performance is apparently designed to discourage arguments for the severest measure of banning sales of that type of vehicles.

The dramatic auto policy change represents a grave situation for the auto industry in which automakers' growth and prosperity are at stake. Given that the auto industry has a broad industrial base, the auto policy change may have great implications for national economic growth and employment. At the same time, however, the policy change could exert a very great impact on the global oil industry and market.

Since last year, a peak oil demand theory has attracted much attention in the oil industry. Behind the theory have been remarkable improvements in electric vehicles' performance and their diffusion stimulated by cost reduction. Until recently, however, a mainstream view was that oil demand would not peak before 2040 because gasoline and diesel vehicles would still be competitive with their demand remaining strong, even though with auto fuel demand growth plunging on the diffusion of electric and other clean vehicles, and demand for ship and aircraft fuel and petrochemical materials would expand.

However, such mainstream view might have failed to assume a gasoline and diesel vehicle sales ban in such major countries as Britain and France. The ban is a new key factor for analyzing global oil demand and the international oil market. As a matter of course, it is uncertain how such auto sales ban would be implemented and become more feasible. Future attention should be paid to whether the policy would spread further and be enhanced in the world. In addition, a key point is that the policy's impact, if any, will emerge not immediately but over a long term.

Nevertheless, the policy's potential impact on demand for vehicle fuel as a dominant component of overall oil demand may have great repercussions. It may be a new factor that the global oil industry and oil producing countries cannot ignore. In the global oil market and industry over several recent years, the shale revolution on the supply side has attracted much attention as a game changer. So far, we have analyzed oil supply problems and the oil market under the paradigm that oil demand would continue to grow over a long term. If the paradigm changes, however, it may have a very great impact.

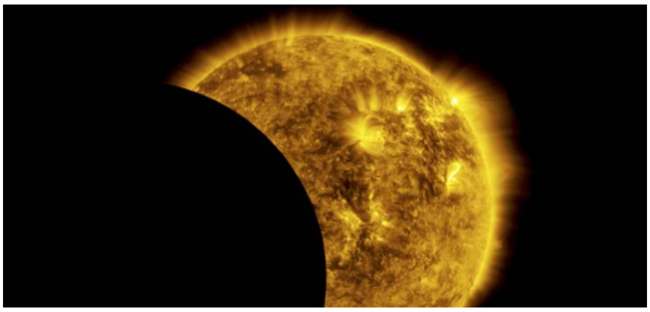
In thinking about the long-term future of oil that has the largest share of the global energy mix and is the most important commodity for international trade, we must pay much attention to auto policy and strategy changes as an emerging uncertain factor and to its impact.

CAN SATELLITES THAT CAUSE ARTIFICIAL ECLIPSES HELP FIND OTHER PLANETS?

「人工日蝕」能否幫助我們找到外星生命？

By Taylor Kubota, August 8, 2017

In our hunt for Earth-like planets and extraterrestrial life, we've found thousands of exoplanets orbiting stars other than our sun. The caveat is that most of these planets have been detected using indirect methods. Similar to how a person can't look at anything too close to the sun, current telescopes can't observe potential Earth-like planets because they are too close to the stars they orbit, which are about 10 billion times brighter than the planets that surround them.



A possible solution might be to create an artificial solar eclipse with two precisely positioned spacecraft, according to Simone D'Amico, assistant professor of aeronautics and astronautics at Stanford and director of the Space Rendezvous Laboratory. One craft –

known as a starshade – would position itself like the moon in a solar eclipse, blocking out the light of a distant star, so a second spacecraft with a telescope could view the nearby exoplanets from within the shadow cast by the starshade.

"With indirect measurements, you can detect objects near a star and figure out their orbit period and distance from the star," said D'Amico, whose lab is working on this eclipsing system**.** "This is all important information, but with direct observation you could characterize the chemical composition of the planet and potentially observe signs of biological activity – life."

Going small

Proposed observatories capable of imaging Earth-like planets require a starshade tens of meters in diameter separated from the telescope by a distance equal to multiple Earth diameters, and the formation would have to be deployed beyond Earth orbit. Altogether, this mission would cost billions of dollars. Instead of sending a pricey, untested system into space, D'Amico's lab, in collaboration with exoplanet expert Bruce Macintosh, professor of physics, has created a smaller version of this formation, likely to cost millions rather than billions. The primary objective of this mission is to provide a low-cost flight demonstration of starshade technology to increase the confidence of the scientific community in the capabilities of a full-scale observatory.

"So far, there has been no mission flown with the degree of sophistication that would be required for one of these exoplanet imaging observatories," said Adam Koenig, a graduate student in the Space Rendezvous Laboratory. "When you're asking headquarters for a few billion dollars to do something like this, it would be ideal to be able to say that we've already flown all of this before. This one is just bigger."

Called mDOT for miniaturized distributed occulter/telescope, the system includes two parts: a 3-meter diameter starshade on a 100-kilogram microsatellite and a 10-centimeter diameter telescope on a 10-kilogram nanosatellite. The starshade and telescope will be deployed in high Earth orbit with a nominal separation of less than 1,000 kilometers.

The shape of the starshade in mDOT is based off research by Robert Vanderbei of Princeton University, reformulated by the Space Rendezvous Laboratory in order to fit the constraints of a much smaller spacecraft. At launch, the starshade will be folded along the sides of the dishwasher-sized microsatellite. Once in orbit, the sharshade will unfold into a flower-like shape.

"With this special geometric shape, you can get the light diffracting around the starshade to cancel itself out," explained Koenig. "Then, you get a very, very deep shadow right in the center. The shadow is deep enough that the light from the star won't interfere with observations of a nearby planet."

Accurate, autonomous navigation

The shadow produced by mDOT's starshade is only tens of centimeters in diameter, which means the telescope's lateral position relative to the starshade has to be controlled to within about 15 centimeters.

In their design, the researchers have both spacecraft fly in a large orbit with the starshade eclipsing the target star at the point of the orbit that's farthest from Earth – the point at which the spacecraft are moving the slowest relative to each other. After about an hour of this tight positioning, they will allow the formation to break up until it's nearly time for the spacecraft to line up again for the next observation. The researchers expect to need tens of hours of observation time to demonstrate that the starshade is working as intended.

Due to the challenging requirements, the only way to realize mDOT is through an autonomous system that is not affected by the communication delays between the satellites and the mission operators on Earth. Autonomous spacecraft formation-flying is the research focus of D'Amico's Space Rendezvous Laboratory.

New science and technology demonstration

The miniaturized mDOT won't be able to resolve Earth-like planets because they are still too close to their parent stars. It could, however, give us a direct glimpse at another star system's equivalent of Jupiter or help characterize exozodiacal dust concentrations around nearby stars, which is a priority for NASA.

This is one of D'Amico's several projects focused on better understanding Earth and the universe with the assistance of precision formation-flying spacecraft. Two current missions he helped with are GRACE and TanDEM-X, which are measuring changes in Earth's gravity field and shape, respectively. The lab is also working on larger formations of spacecraft called swarms. However, similar to mDOT, before these technologies can be flown, it is necessary to prove that they work as expected using testbeds on the ground. To this end, D'Amico has built a facility that precisely replicates the complex and unique illumination conditions encountered by sensors in space (see video).

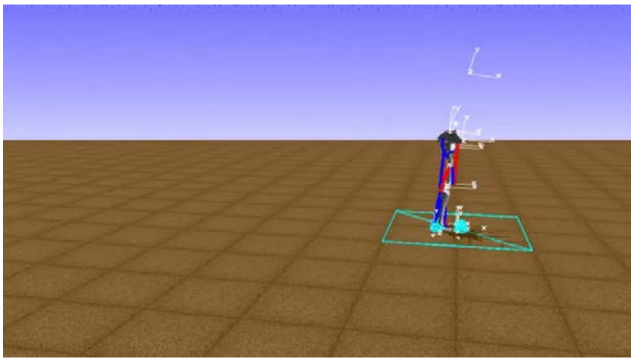
"I'm enthusiastic about my research program at Stanford because we're tackling important challenges," said D'Amico. "I want to help answer fundamental questions and if you look in all current direction of space science and exploration – whether we're trying to observe exoplanets, learn about the evolution of the universe, assemble structures in space or understand our planet – satellite formation-flying is the key enabler."

HOW DO PEOPLE RELEARN TO WALK AFTER SURGERY?

手術之後，如何再次學會走路？

By Nathan Collins, August 14, 2017

At this moment, computer-generated skeletons are competing in a virtual race, running, hopping and jumping as far as they can before collapsing in an electronic heap. Meanwhile, in the real world, their coaches – teams of machine learning and artificial intelligence enthusiasts – are competing to see who can best train their skeletons to mimic those complex human movements. Perhaps the coaches are doing it for glory or prizes or fun, but the event's creator has a serious end goal: making life better for kids with cerebral palsy.



Łukasz Kidziński, a postdoctoral fellow in bioengineering, dreamed up the contest as a way to better understand how people with cerebral palsy will respond to muscle-relaxing surgery. Often, doctors resort to surgery to improve a patient's gait, but it doesn't always work.

"The key question is how to predict how patients will walk after surgery," said Kidziński. "That's a big question, which is extremely difficult to approach."

Modeling the walk

Kidziński works in the lab of Scott Delp, a professor of bioengineering and of mechanical engineering who has spent decades studying the mechanics of the human body. As part of that work, Delp and his collaborators have collected data on the movements and muscle activity of hundreds of individuals as they walk and run.

With data like that, Delp, Kidziński and their team can build accurate models of how individual muscles and limbs move in response to signals from the brain.

But what they could not do was predict how people relearn to walk after surgery – because, as it turns out, no one is quite sure how the brain controls complex processes like walking, let alone walking through the obstacle course of daily life or relearning how to walk after surgery.

"Whereas we've gotten quite good at building computational models of muscles and joints and bones and how the whole system is connected – how the human machine is built – an open challenge is how your brain orchestrates and controls this complex dynamic system," Delp said.

Machine learning, a variety of artificial intelligence, has reached a point where it could be a useful tool for modeling of the brain's movement control systems, Delp said, but for the most part its practitioners have been interested in self-driving cars, playing complex games like chess or serving up more effective online ads.

"The time was right for a challenge like this," Delp said, in part because some in the machine learning community are looking for more meaningful problems to work on, and because bioengineers stand to gain from understanding more about machine learning. His lab's most successful efforts to model human movement have come from efforts to represent neural control of movement, Delp said, and machine learning is likely a realistic way to think about learning to walk.

The contest

So far, 63 teams have submitted a total of 145 ideas to Kidziński's competition, which is one of five similar contests created for the 2017 Neural Information Processing Systems conference. Kidziński supplies each team with computer models of the human body and the world that body must navigate, including stairs, slippery surfaces and more. In addition to external challenges, teams also face internal ones, such as weak or unreliable muscles. Each team is judged based on how far its simulated human makes it through those obstacles in a fixed amount of time.

Kidziński and Delp hope that more teams will join their competition, and with about two months remaining, they hope that at least a few teams will overcome all the various virtual obstacles thrown in their way. (No one has done so yet – the top teams have for the most part conquered walking, but none has attempted the more athletic maneuvers.) The challenge, Kidziński said, is "very computationally expensive."

In the long run, Kidziński said he hopes the work may benefit more than just kids with cerebral palsy. For example, it may help others design better-calibrated devices to assist with walking or carrying loads, and similar ideas could be used to find better baseball pitches or sprinting techniques.

But, Kidziński said, he and his collaborators have already created something important: a new way of solving problems in biomechanics that looks to virtual crowds for solutions.

Delp is the James H. Clark Professor in the School of Engineering and a member of Stanford Bio-X and the Stanford Neurosciences Institute. Graduate student Carmichael Ong, postdoctoral fellow Jason Fries, Mobilize Center Director of Data Science Jennifer Hicks and Mohanty Sharada coordinated the project. Sergey Levine, Marcel Salathé and Delp serve as advisors