Abstractions

COLLABORATING AUTHOR

With antibiotic-resistant strains of *Mycobacterium tuberculosis* on the rise, the development of new drugs that combat this bacterium and treat tuberculosis has become an urgent public-health need. Biophysicist Huilin Li of Brookhaven National Laboratory in Upton, New York, has been collaborating for several years on this problem with Carl Nathan, a researcher at Weill Cornell Medical College in New York City. Together they have identified a new class of compounds — oxathiazol-2-ones — that selectively target mycobacteria but not human cells (see page 621). He tells *Nature* about the implications.

How do the compounds work?

They target the mycobacterial ubiquitin-proteasome pathway, which degrades damaged proteins. We don't know exactly how or why, but agents that inhibit the function of proteasomes in mycobacteria kill these pathogens in host cells. It's clear that mycobacteria must get rid of their damaged proteins to survive the hostile environment of the human macrophage cells they infect.

What's the main hurdle to developing proteasome inhibitors of tuberculosis?

The difficulty is finding species-specific inhibitors that target the mycobacterial proteasome without affecting the human one. Proteasomes are protein complexes that are highly conserved from archaebacteria to humans. Dozens of proteasome inhibitors exist, but most inhibit all proteasomes from any cell and any species.

How did you beat the specificity problem?

Our earlier collaboration solved the crystal structure of the mycobacterial proteasome bound to another class of inhibitor. This revealed biochemical and structural differences between the bacterial and mammalian proteasomes, which we exploited to screen for chemical compounds that would bind to only the mycobacterial and not the human proteasome.

Did the compounds have other advantages?

Mycobacteria have a sticky lipid coating full of mycolic acid that prevents a lot of compounds from getting into the bacteria. Our inhibitors go through this cell wall very quickly. Another crucial issue is that many existing anti-tuberculosis drugs target ribosomes, which are not active if the bacteria are not replicating, or 'dormant', and thus not making any new proteins. But dormant bacteria still require active proteasomes. This means that our discovery could lead to compounds that would clear a person of mycobacteria in a way that current treatments do not. ■

MAKING THE PAPER

Makoto Fujita

Crystalline molecular flasks capture chemical reactions.

In a chemical reaction, participating molecules swap components and rearrange their shapes, sometimes taking on forms that last for only a fraction of a second before the final reaction products are formed. Because of the transient, unstable nature of these reaction intermediates, it has been difficult to catch a glimpse of their three-dimensional structures.

But Makoto Fujita and his colleagues at the University of Tokyo may have found a solution. Using a textbook chemical reaction as an example, on page 633 the chemists show how they slowed down the reaction process by trapping the reagents in 'crystalline molecular flasks'. This, in turn, allowed them to capture snapshots of an elusive intermediate by X-ray crystallography.

Fujita had the idea of assembling crystalline molecular flasks in which to carry out chemical reactions several years ago. His team's first attempt consisted of chemical 'cages' crystallized together with a substrate to render that reagent more stable and resilient. "The idea worked quite well, and we carried out some chemical transformations in the cavity of the cage," says Fujita.

But the approach turned out to be impractical: "Having to crystallize the cage for each reaction was not always easy and normally time consuming," says Fujita. To remedy this, he assembled a network of connected cages, or pores, thereby forming a crystalline structure that was stable over a range of temperatures.

"The porous network has a big advantage over the cage because it does not require crystallization each time," says Fujita, who published the first attempt at assembling the network in 1994. By this method, the structure exists as a crystal to which various substrates can simply be added, depending on the reaction being studied.

To test whether the porous network could be used to perceive chemical reactions by X-ray crystallography, Fujita and his colleagues chose a well-known organic reaction between an amine and an aldehyde. The reaction, known as Schiff-base formation, produces a hemiaminal intermediate that is normally very short-lived.

Fujita and his colleagues assembled their porous network embedded with amine, and then immersed it in acetaldehyde. Once both molecules met in a single pore, the reaction took place — but at a slower pace than normal. "The reaction times were retarded within the pore because of steric [space] restrictions. Reactions could also be paused at any time by cooling the crystal to liquid-nitrogen temperature, explains Fujita, which enabled the team to obtain structural data for the paused reaction steps.

The biggest challenge, he says, was to optimize the reaction conditions, such as crystal quality, solvent, temperature and reaction time. In particular, they had to tweak conditions so that the concentration of the hemiaminal intermediate was more than 35% within the porous network. Once achieved, "We finally succeeded in observing hemiaminal by X-ray crystallography", he says.

Although the structure of the hemiaminal intermediate was not itself that surprising, the study demonstrates a useful approach for analysing chemical-reaction intermediates. Fujita is now forging ahead to examine more unusual structures, such as the intermediates formed during organometallic transformations or enzymatic reactions with transition-metal ions, some of which, he says, have never been observed. ■

FROM THE BLOGOSPHERE

With advances in publishing technologies come new job titles. On the Sceptical Chymist blog's popular question-and-answer series 'Reactions', Laura Croft, technical editor for *Nature Chemistry* and *Nature Chemical Biology*, describes her own role (http://tinyurl.com/yb5vvyg).

Technical editors, she says, are in charge of "adding extra features to research articles on our website. We are incorporating extra compound information pages, which are linked from bold compound numbers in the HTML and PDF of our articles, as well as highlighting chemical names in the text and linking these to free chemical databases." She hopes her efforts will eventually change the way scientists use and retrieve information online.

The interview also touches on Croft's interest in the chemistry of pigments and photographic techniques, and how she would have liked to have eaten dinner with William Perkin, the English chemist who discovered a purple dye in 1856, aged just 18. She thinks Reactions should interview Stuart Warren, a co-author of "the big green book", the textbook from which she learned most of her organic chemistry. ■

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