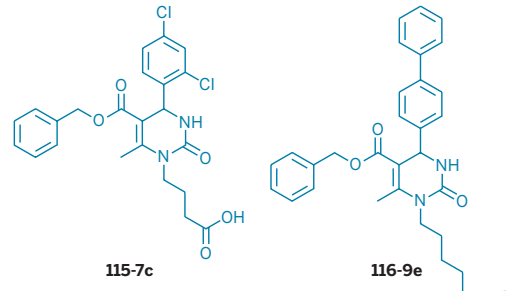
SIMILAR MOLECULES, OPPOSITE EFFECTS

PROTEIN INTERACTIONS: Small-molecule analogs affect heat-shock protein complex in different ways

RESEARCHERS HAVE SOLVED the mystery of the opposing effects—activation and inhibition—of two similar small organic molecules on bacterial heat-shock protein 70 (Hsp70), a molecular chaperone involved in protein folding and other cell functions.

The work, carried out by Jason Gestwicki of the University of Michigan, a specialist in multiprotein complexes, and coworkers, could lead to a better understanding of how Hsp70 works on the molecular level. New insights about Hsp70 are important because of its emerging roles in cancer, infection, and neurodegenerative disease. The work also provides a road map for obtaining contrasting biological effects from the same small-molecule chemical scaffold (*ACS Chem. Biol.*, DOI: 10.1021/cb1000422).



These small molecules are closely related structurally, but one activates (left) and the other inhibits (right) Hsp70.

Two years ago, Gestwicki's group, in collaboration with two University of Pittsburgh groups led by chaperone expert Jeffrey L. Brodsky and organic synthesis specialist Peter Wipf, identified two small molecules that affect Hsp70. One molecule, called 115-7c, activates the chaperone, and the related compound, 116-9e, inhibits it, both in vitro and in living cells. The researchers were astonished that two similar small molecules could have such contradictory effects on the same system.

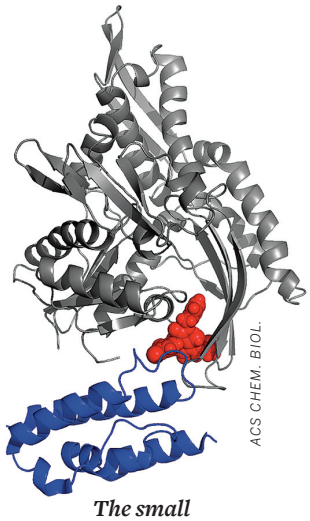
Now, Gestwicki and coworkers have used NMR, mutagenesis, and other techniques to understand how this happens. Surprisingly, the study shows that 115-7c and 116-9e bind at the same protein-protein interface—one formed when Hsp70 is bound by Hsp40, a "cochaperone" that regulates Hsp70's activity.

Compound 115-7c binds at the Hsp40-Hsp70 interface and appears to cooperate with Hsp40 to activate Hsp70. The other agent, 116-9e, doesn't activate the chaperone. Instead it blocks Hsp40-Hsp70 binding, effectively inhibiting the chaperone system.

It's unusual to find druglike agents with any effect on protein-protein interfaces, which are generally too large to be disrupted by small molecules, but it's unheard of for such similar chemical agents to have opposite effects. "We don't know of any other examples" in which a single small-molecule scaffold such as the one shared by 115-7c and 116-9e affects a protein-protein interface in reverse ways, Gestwicki says.

Although the effects of the two chemical probes "are modest, they are very promising and may help identify novel allosteric sites that could eventually be structurally characterized to help develop more potent molecules," says chemical biologist Charles S. Craik of the University of California, San Francisco, whose research interests include protein-protein interactions.

Compounds related to 116-9e are currently being tested for activity in mouse models of Alzheimer's disease, Gestwicki says.—STU BORMAN



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The small molecule 115-7c (orange) and a domain of Hsp40 (blue) bind to part of Hsp70 at the same time and activate the chaperone

JAPANESE INDUSTRY Leadership changes at profitable Shin-Etsu Chemical

Shin-Etsu Chemical, Japan's most profitable chemical company, will get a new president after Chihiro Kanagawa, its leader for the past two decades, moves on to become chairman, a position that has been vacant for at least 15 years.

Kanagawa will be succeeded by Shunzo Mori, who is currently executive vice president in charge of human resources and general administration. Mori, 72, joined Shin-Etsu in 1963, one year after Kanagawa, who is now 84. Trained as a mechanical engineer, Mori managed a Japanese rare-earth compound and silicone plant in the early 1990s. After that, he headed the company's electronic materials business for several years.

Shin-Etsu did not provide a reason for the senior management change but emphasized that it plans no major rethink of how the company is run. The firm is the world's largest producer of both polyvinyl chloride resins and silicon wafers, two businesses in which it intends to maintain its global dominance.

With net earnings of nearly $900 million in its latest fiscal year, Shin-Etsu is far and away Japan's most profitable chemical company (C&EN, May 17, page 11). Asahi Kasei, the country's second most profitable chemical maker, managed less than a third of Shin-Etsu's profit last year despite sales that were 50% greater. For the 14 years up to the global downturn that started in 2008, Shin-Etsu posted record earnings every year.

It's not clear how much influence over the company Kanagawa will have as chairman, but he once said that he planned to lead the firm until he is 100 (C&EN, Oct. 7, 2002, page 18).—JEAN-FRANÇOIS TREMBLAY