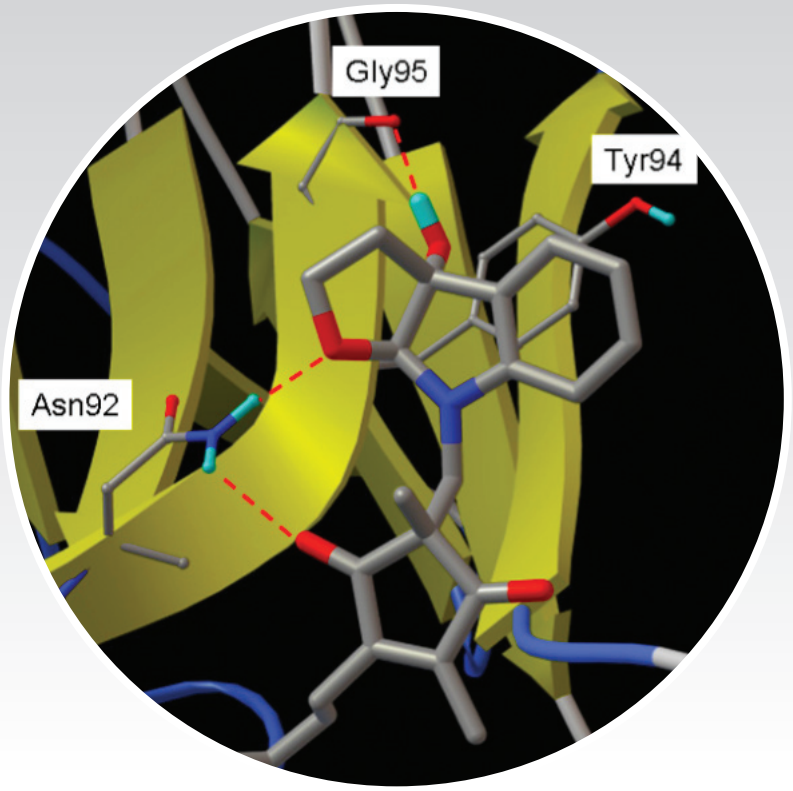
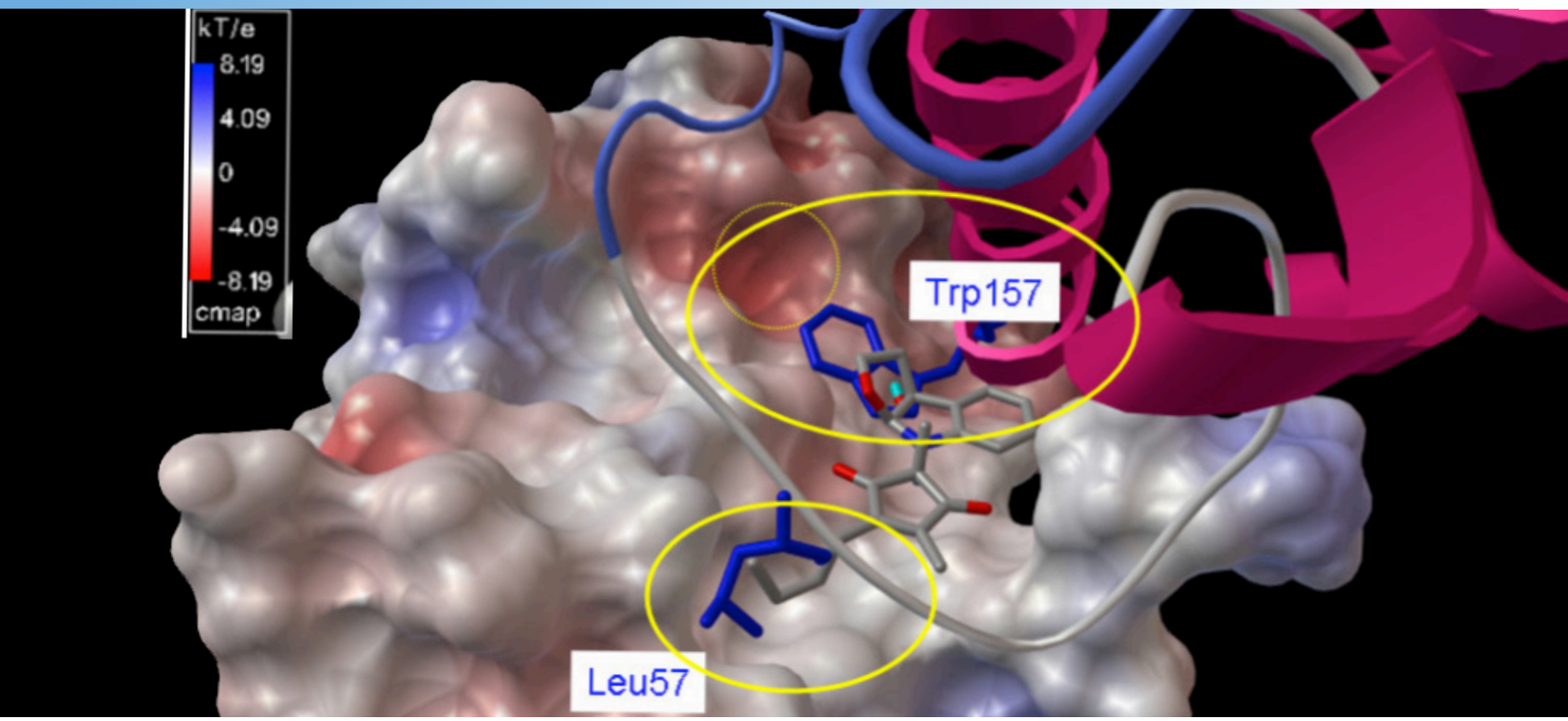


A simulation created at the Ohio Supercomputer Center by Chenglong Li illustrates MDL-A (ball-and-stick) binding with a section of GP130 (yellow ribbon). Li is using fragment-based drug design to find potential solutions to suppressing Interleukin-6.

Biological Sciences

Ohio's bioscience researchers are gathering and analyzing vast amounts of genetic, molecular and environmental data to target diagnosis and treatment of disease, improve understanding of intricate systems and optimize valuable biological traits. For example, a biophysicist is manipulating simulated enzyme fragments to create potent, new cancer-fighting drug candidates. Another scientist is studying a strain of bacteria that has the potential to provide light in alternative environments. And, a chemist is developing techniques to help combatants fight off the deadly effects of neurotoxins. More than 1,345 bioscience-related organizations call Ohio home, employing more than 62,000 highly skilled workers, according to BioOhio, a nonprofit industry association. The following pages illustrate just a few examples of cutting-edge biosciences research supported by Ohio Supercomputer Center resources and services.



above: An electrostatic representation (red: negative; blue: positive; white: hydrophobic) created at the Ohio Supercomputer Center by Ohio State's Chenglong Li shows the immune-response messenger IL-6 in ribbon representation. Two yellow ellipses indicate binding "hot spots" between IL-6 and the common signal-transducing receptor GP130.

Li leverages fragment-based drug design to **block cancer precursor**

The human body normally produces an immune-response messenger known as Interleukin-6 (IL-6) to combat infections, burns and traumatic injuries. Scientists have found, however, that in people who have breast or prostate cancer, the body fails to turn off the response and overproduces the protein molecule IL-6, causing inflammation.

"There is an inherent connection between inflammation and cancer," explained Chenglong Li, Ph.D., an associate professor of medicinal chemistry and pharmacognosy at The Ohio State University (OSU). *"In the case of breast cancers, a medical review systematically tabulated IL-6 levels in various categories of cancer patients, all showing that IL-6 levels elevated up to 40-fold."*

In 2002, Japanese researchers found that madindoline A (MDL-A) could be used to mildly suppress the IL-6 signal. About the same time, Stanford scientists constructed a static image of the crystal structure of IL-6 and two related proteins. Li recognized the potential of these initial insights and partnered with an organic chemist and a cancer biologist at OSU's James Cancer Hospital to investigate further, using Ohio Supercomputer Center systems to construct malleable, three-dimensional color simulations of the protein complex.

Li simulated IL-6 and the two additional helper proteins: receptors IL-6R and GP130. Two full sets of the three proteins often combine to form a six-sided "hexamer" to transmit signals that will, in time, cause cellular inflammation. Li defined the interactions between those proteins and the strength of their binding at five 'hot spots' found in each half of the IL-6/IL-6R/GP130 hexamer.

By plugging small molecules, like MDL-A, into any of those hot spots, Li would be able to identify the most effective binding site for blocking the formation of the hexamer. So, he examined the binding strength of MDL-A at each of the hexamer hotspots, identifying the most promising location, which turned out to be between IL-6 and the first segment, or modular domain (D1), of the GP130 protein.

To design even more effective derivatives of MDL-A that would dock with D1 at that specific hot spot, Li searched through more than 6,000 drug fragments, identifying two potential solutions by combining the "top" half of the MDL-A molecule with the "bottom" half of a benzyl or a pyrazole fragment. These candidates preserve the important binding features of the MDL-A, while yielding molecules with stronger molecular bindings that also are easier to synthesize than the original MDL-A.

"We're making excellent progress," said Li. *"The current research offers us an exciting new therapeutic paradigm: targeting the tumor microenvironment and inhibiting tumor stem cell renewal, leading to a really effective way to overcome breast tumor drug resistance, inhibiting tumor metastasis and stopping tumor recurrence."* ■

Project lead: Chenglong Li, The Ohio State University
Research title: Designing drugs to stop IL-6 signaling for anti-cancer therapy
Funding source: Department of Defense
Web site: pharmacy.osu.edu/programs/medchem/faculty/chenglong_li/