PHARMACEUTICAL INFORMATICS

MORGRIDGE
INSTITUTE FOR RESEARCH

Accelerating the search for a new generation of medicines starts at the molecular level

An aging population, changing environment and growing resistance to existing medicines make answering the challenges of pharmaceutical development more urgent than ever before. While optimism remains strong for the eventual cure of diseases such as Parkinson's, Alzheimer's and diabetes, the need for new drugs to manage symptoms and slow disease progression will exist for decades to come. At the same time, changing environmental factors and increased human mobility abet the transmission of diseases, including the spread of pathogens with genetic resistance to current pharmaceutical treatments.

Solutions to these challenges are to be found at the molecular level. Pharmaceutical informatics uses information technology and computational chemistry to analyze the characteristics of billions of interactions among proteins and drug-like molecules to find optimal pairs that will bind for healthful benefits. Proteins typically form three-dimensional or "folded" structures. However, as a manifestation of the disease process, misfolding may occur, rendering key proteins dysfunctional. The active ingredients in medicines are small molecules that moderate problematic proteins or restore normal function to achieve therapeutic benefits.

The identification of new and optimal molecular level interactions will speed the development of drugs and treatment procedures that promise significantly improved outcomes for patients suffering from cancer and other diseases. Researchers in pharmaceutical informatics at the Morgridge Institute are focusing initial efforts on pioneering the design of a new generation of anti-cancer drugs that will kill tumor cells while boosting the complementary healing role of the immune system.

Expertise in molecular design of cures: Fernández and Kim

Ariel Fernández serves as the principal scientist for pharmaceutical informatics at the Morgridge Institute. A native of Bahía Blanca, Argentina, Fernández is an internationally recognized expert in the molecular design of anti-cancer drugs. He previously held the Karl F. Hasselmann Chair in Engineering at Rice University, where he also was a professor of bioengineering. He holds a Ph.D. in chemistry from Yale University and conducted postdoctoral research with Nobel Laureate Manfred Eigen at the Max Planck Institute for Experimental Medicine in Göttingen, Germany. With groundbreaking insights derived from his knowledge of physical chemistry, Fernández is leading a transformation in cancer therapy based on computer-aided redesigns of current anti-cancer drugs to moderate toxicity and other adverse side effects.

The immense challenge of integrating the torrent of data and information to form a delivery strategy is addressed by cyberinfrastructure expert Sangtae Kim. A native of Korea who grew up in Montreal, Canada, Kim is the information architect for the pharmaceutical informatics team in addition to his primary leadership role as executive director of the Morgridge Institute. Prior to this appointment, Kim was the Donald W. Feddersen Distinguished Professor at Purdue University. Previously, he served as director of the cyberinfrastructure division at the National Science Foundation and held vice president positions with pharmaceutical companies Eli Lilly and Warner Lambert. He started his career as a faculty member in chemical engineering at the University of Wisconsin–Madison and was elected in 2001 to the National Academy of Engineering for pioneering contributions to computational methods in drug discovery. Kim received concurrent bachelor's and master's of science degrees from Caltech and earned his Ph.D. from Princeton.

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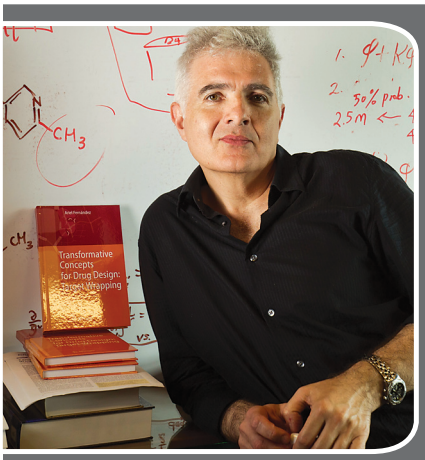

Ariel Fernández
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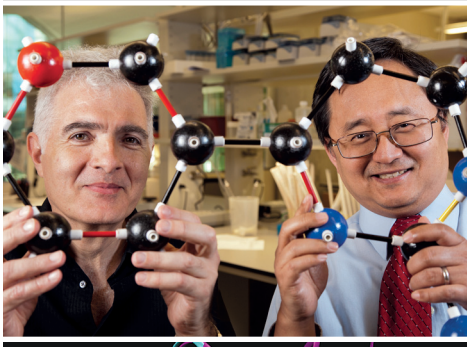

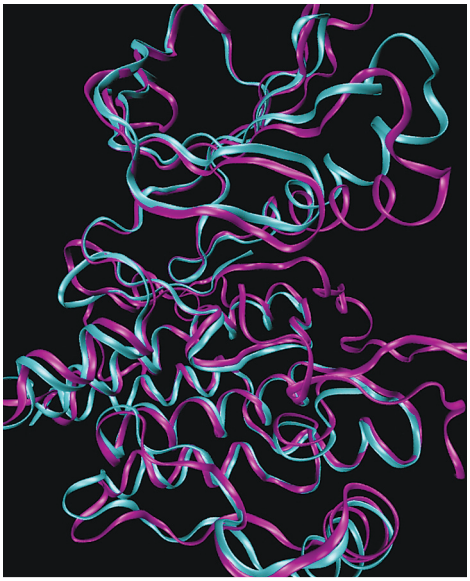

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Discovery of unique bonding properties opens door to better drug design

A fundamental indicator of success in drug development lies in the ability to predict whether a given molecule will bind to a target and if so, how selectively. Yet challenges related to proper binding are among the most significant hurdles in drug development today. Specifically, while scientists may be able to manipulate molecules to increase their attraction to a desired target, in the process, these molecules also become more likely to link with other, unintended targets. Tissue damage and other adverse side effects from these unintended linkages often render potential new medicines unusable.

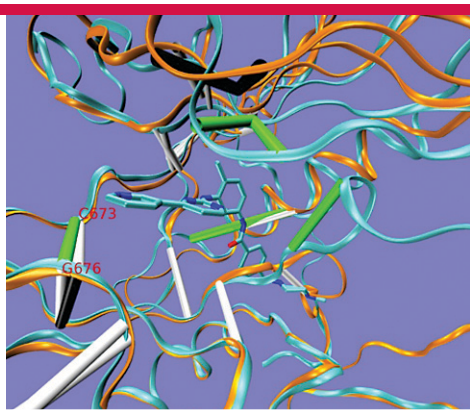
Recent discoveries by Fernández and his colleagues relating to protein interactions with water have led to important new insights about molecular binding with major implications for the pharmaceutical industry. Fernández has identified a special attribute of hydrogen bonds within proteins that opens the door to molecular engineering and the design of specific, targeted interactions. These special hydrogen bonds—known as dehydrons—seek shielding from the surrounding water by attracting and binding to drug-like molecules. In addition to this "sticky" bonding capability, the unique pattern of dehydrons makes them excellent drug targets to distinguish cancer-causing proteins from proteins essential for life processes in healthy cells. Molecules designed to bind selectively with cancer dehydrons would be less likely to bind with unintended structures so the risk of adverse effects would be minimized.

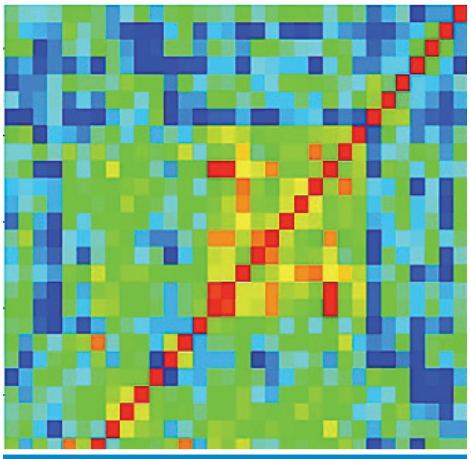
What is the hope?

Scientists at the Morgridge Institute anticipate a golden age for progress in cancer research thanks to a series of interdisciplinary advances that allow for greater analytical capabilities and more rational drug development strategies than ever before. In recent years, the pharmaceutical industry has launched an impressive array of new anti-cancer drugs, yet each has encountered limitations including drug resistance and adverse side effects. The pharmaceutical informatics team at the Morgridge Institute is working to provide a scientific basis for understanding and overcoming these limitations. In particular, a "dehydron wrapping" technology based on the work of Fernández is expected to allow for tailored binding and modulation of cancer proteins without damaging healthy proteins. The technology will support creation of a new generation of anti-cancer drugs that work in tandem with immunotherapy to boost survival rates for cancer patients.

How the Morgridge Institute for Research will make a difference

With its focus on accelerating the "discovery to delivery" of scientific breakthroughs to improve human health, the Morgridge Institute for Research is strategically positioned to translate basic research such as the discovery of the dehydron into new therapies and cures. The superior computational resources and cutting-edge analytical tools available to the institute's scientists ensure the pharmaceutical informatics team is well-equipped to address challenges that have stalled progress in otherwise promising avenues of investigation. At the same time, the private, nonprofit structure of the Morgridge Institute for Research provides the flexibility needed to attract and retain exceptional scientific talent. The collaborative approach to research at the institute and its public twin, the Wisconsin Institute for Discovery, also affords the pharmaceutical informatics team with unparalleled opportunity to explore groundbreaking, interdisciplinary concepts with the support of leading experts in complementary fields. To learn more, visit www.morgridgeinstitute.org.





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