Commercializing structural biology knowledge can save money and speed drug discovery

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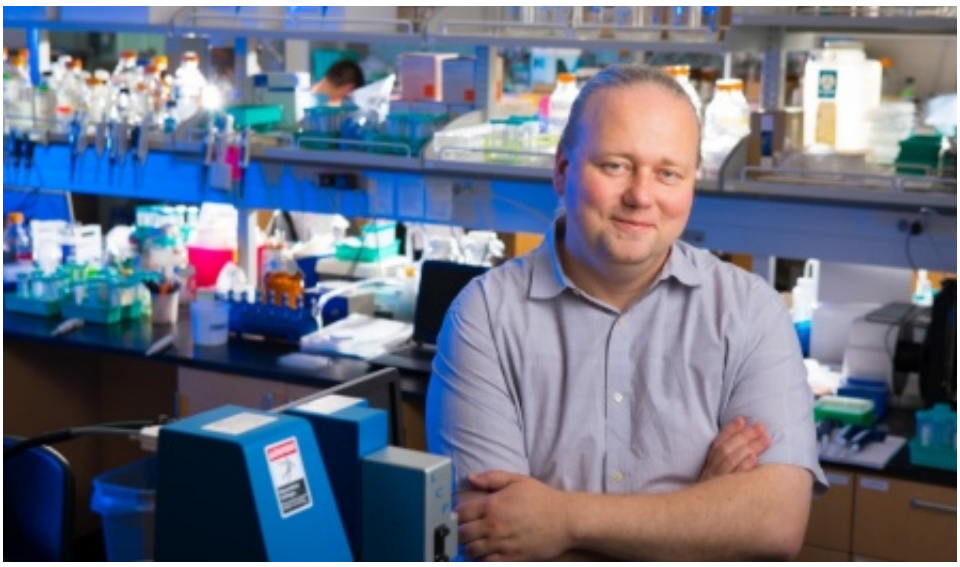

Artem Evdokimov, the CEO and chief science officer at HarkerBIO. Credit: Douglas Levere

HarkerBIO is a "shining star" in the growing biotech ecosystem taking shape on the Buffalo Niagara Medical Campus. The small structural biology company determines 3-D structures of proteins for drug and biotech companies.

That may sound straightforward – even simple – but the process is something right out of Star Trek. HarkerBIO uses sophisticated

biochemical techniques, supercomputing power and laboratory expertise to decipher the giant, complex structures of proteins.

The company then uses that information to help pharmaceutical companies sleuth out sites where drug-like molecules may bind, eventually creating molecules for new medicines. Biotech companies, meanwhile, use the structural data to improve enzyme catalysts that hasten difficult chemical transformations.

HarkerBIO was formed in 2015 by Hauptman-Woodward Medical Research Institute, which is home to the Department of Structural Biology at the Jacobs School of Medicine and Biomedical Sciences at UB, to commercialize Hauptman-Woodward's expertise in X-ray crystallography.

It now has 14 employees, participates in the START-UP NY economic development program and has a partnership with Albany Molecular Research Inc., a contract research and manufacturing organization with a lab on the medical campus.

Drug discovery

"When you're discovering a drug, you have a lot of small molecules to choose from. You have quintillions of options… more than all the stars in the universe," said Artem Evdokimov, PhD, the CEO and chief science officer at HarkerBIO. "But only a few are good. The rest are not useful."

One way to find molecules that attach to proteins is to simply try them all. Today companies can experimentally test several million different molecules to find out if any work.

A much more affordable and flexible method is to screen them in a

virtual world—inside a computer. To do this, scientists probe a three-dimensional structure of the protein (with tens of thousands of atoms or more) with billions of virtual chemicals inside a computer simulation. When some of the virtual compounds "stick" to the protein structure, they can be made by chemists in a laboratory and then tested to see if they actually bind. Thus, the number of molecules that need to be made and tested is reduced from millions to hundreds or less.

"Ultimately, molecules will get made by a chemist and then tested," Evdokimov said. "Drug design is a cyclic process. You find something that sort of works, and you study it and you change it, and then you make it better."

Commercializing expertise

In the small but competitive world of structural biology, HarkerBIO has an advantage in its specialization. HarkerBIO's scientists consult with prospective customers to discuss their needs and goals in-depth. Sometimes if the project is too challenging, HarkerBIO will help the client define the goals to be more realistic.

"Structural biology is unique in one way," said James Biltekoff, executive chairman of the company. "There is a huge economic benefit to our clients in getting to 'no.' If an idea is a bust, let's find out before they spend $10 or $20 million. Structure is hard data that can tell you whether or not something is going to work."

The long-range goal of the company is to maintain the high-level focus on structure and enhance its role as a "knowledge partner," Biltekoff said.

"And we want to add on a more propriety research function, focused on both the drug discovery process, and on the techniques that we use in

structural biology," he said.

That includes devoting staff time to discovery. "My vision for the company is that all the senior people should eventually be able to use 15 percent of their time on intellectual pursuits," he said.

Capturing proteins

Scientists at HarkerBIO must first get a sample of the target protein. This is accomplished by making cultured cells (bacteria, yeast, insect or human cells) into little factories that produce the protein of interest. Then the protein is purified from cellular extracts and crystallized. Typical protein crystals are less than a tenth of a millimeter long, invisible to the naked eye. These tiny protein crystals must be fished out of their growth solution—by hand, under a microscope—and quickly frozen in liquid nitrogen.

"Trying to crystalize a protein is very, very hard. Proteins have irregular and floppy shapes, like a teddy bear" Evdokimov said. "Imagine piling hundreds of plushy bears in a heap—you just get an irregular pile, not regular arrays like crystals—and that's what has to happen with protein molecules in order for us to study them."

Once a protein is successfully crystalized, it is sent to a government-owned synchrotron facility: a loop three miles in diameter where electrons are blasted around in a vacuum to create a super bright X-ray beam that is focused on the crystal. X-rays are diffracted by the crystal forming a pattern of spots that can be mathematically interpreted into the exact atomic structure of the protein molecule.

Cost of structural work varies from thousands to hundreds of thousands of dollars, depending on the complexity of the proteins. There are other companies that do similar work, but Evdokimov said HarkerBIO has a

very high success rate that companies desire.

Shining star

"HarkerBIO is one of our bright shining stars," said Kim Grant, business development executive at UB's New York State Center of Excellence in Bioinformatics and Life Sciences. "They cut cost out of drug development research."

Laura Sailor, HarkerBIO's corporate development officer, said the company is making a name for itself.

"We are getting recognized on both coasts, by large pharma, biotechs and virtuals," she said. "Adding structural biology in the lead discovery program early on will accelerate your timelines and give you less failures."

"Our edge is that we understand structure and thus function. It is the loss or gain of function that can result in disease," Sailor added. "We sell the insight, structural insight for designing drugs or mechanisms for action."

"We only do structure. We are the structure people."

Provided by University at Buffalo

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