

Collaboration drives achievement in protein structure research

September 15 2014

When this week's print issue of the journal *Science* comes out, a collective cheer will go up from New Mexico, Montana and even the Netherlands, thanks to the type of collaborative effort that is more and more the norm in these connected times. Yes, the research was brilliant, and if we're lucky, it will produce innovations in biology, medicine, biotechnology and agriculture. It could save lives, and it happened because this scientist talked with that one, that one knew another one, and brilliant minds overcame geographic distance to advance human understanding.

"It is tremendously exciting working with researchers around the world, helping them apply the software and algorithms that we have developed to see the inner workings of molecular machines," said Thomas Terwilliger, a senior Los Alamos scientist and Laboratory Fellow.

In this case, researchers at Montana State University have provided the first blueprint of a bacterium's "molecular machinery," showing how bacterial immune systems fight off the viruses that infect them. By tracking down how bacterial defense systems work, the scientists can potentially fight infectious diseases and genetic disorders. The key is a repetitive piece of DNA in the [bacterial genome](#) called a CRISPR, for Clustered Regularly Interspaced Short Palindromic Repeats.

The bacterial genome uses the CRISPR to capture and "remember" the identity of an attacking virus, and now the scientists have created programmable molecular scissors, called nucleases, that are being

exploited for precisely altering the DNA sequence of almost any cell type of interest.

The Los Alamos National Laboratory connection is the development of some terrifically clever software, called SOLVE/RESOLVE and PHENIX, in the protein structure analysis of the nuclease. That, connected with the science-community outreach whereby Los Alamos worked directly with structural biologists worldwide on their problems, helped it all come together. Determining the structure of the nuclease is key to understanding its function.

Los Alamos creates advanced algorithms for determining the structures of proteins and other macromolecules, and the software that makes these algorithms easy to use for thousands of structural biologists worldwide. The Laboratory partners with Lawrence Berkeley National Laboratory, Duke and Cambridge universities to create Phenix, a user-friendly and comprehensive software system that guides users through all the complicated steps necessary to determine the 3-D structure of their macromolecule.

"One of the best parts of working on the Phenix software is that there is a close-knit team of 15 researchers who work closely together, emailing each other many times every day, to make the software work as smoothly and effectively as possible," said Terwilliger.

"Some 13,000 scientific papers have used our SOLVE/RESOLVE and Phenix software," Terwilliger said, and Los Alamos researchers teach crystallographic methods and software tips extensively at scores of workshops around the world. The software licenses, through technology transfer programs, have generated approximately \$3M in licensing revenue.

With the new Montana-based research, "therapies that were

unimaginable may be possible in the future," said Blake Wiedenheft, senior author of the paper and assistant professor in MSU's Department of Microbiology and Immunology. "We know the genetic basis for many plant, animal, and human diseases, and these CRISRP-associated nucleases are now being used in research settings to surgically remove or repair defective genes."

More information: Ryan N. Jackson, Sarah M. Golden, Paul B. G. Van Erp, Joshua Carter, Edze R. Westra, Stan J. J. Brouns, John Van Der Oost, Thomas C. Terwilliger, Randy J. Read, Blake Wiedenheft. Crystal structure of the CRISPR RNA-guided surveillance complex from *Escherichia coli*. *Science*, 2014 [DOI: 10.1126/science.1256328](https://doi.org/10.1126/science.1256328)

Provided by Los Alamos National Laboratory

Citation: Collaboration drives achievement in protein structure research (2014, September 15) retrieved 10 April 2024 from <https://phys.org/news/2014-09-collaboration-protein.html>

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