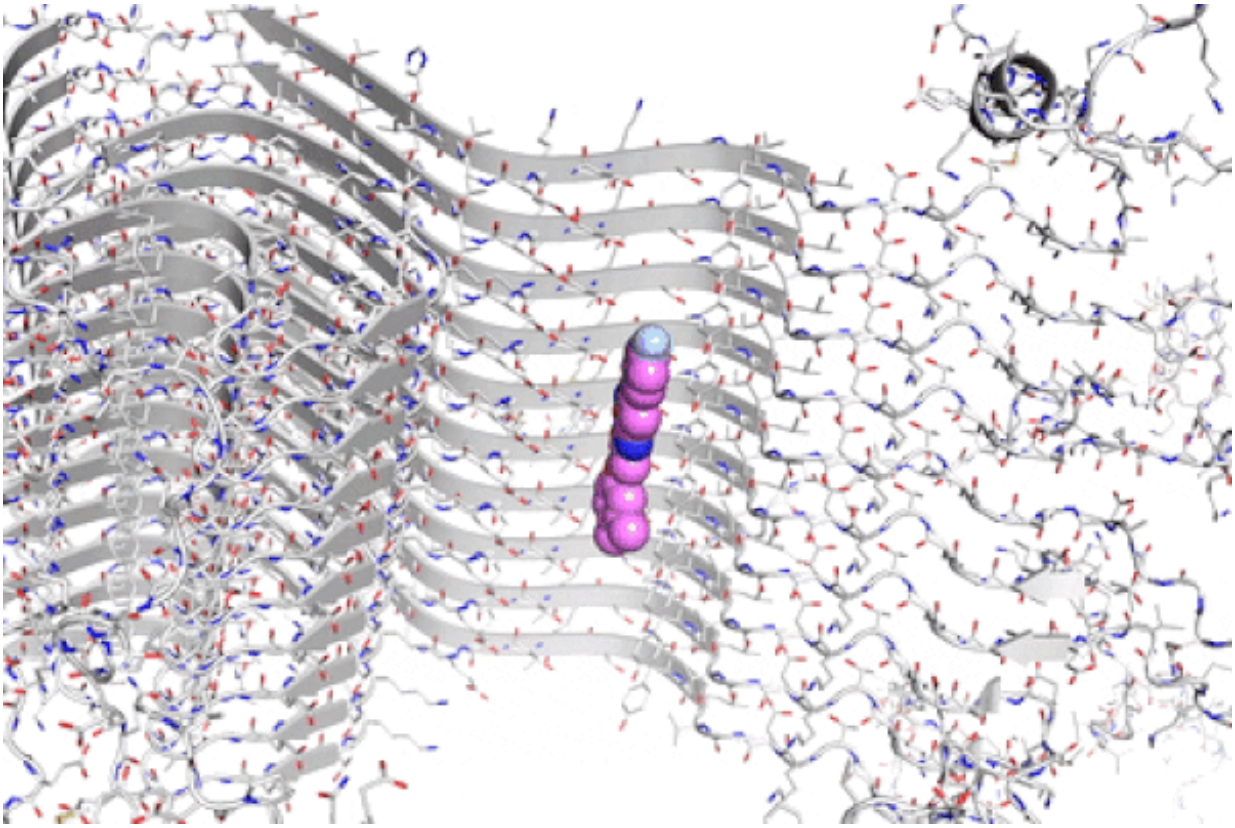
Researchers discover new molecules for tracking Parkinson's disease

September 21 2020, by Erica K. Brockmeier



The chemical structure of an alpha-synuclein fibril with an “exemplar” molecule, shown as colored spheres, bound to a previously identified binding site. Researchers at Penn recently demonstrated a new method for screening and identifying molecules computationally that can then be developed into imaging probes for studying proteins that are associated with Parkinson’s disease. Credit: E. James Petersson

For many of the 200,000 patients diagnosed with Parkinson's disease in the United States every year, the diagnosis often occurs only after the appearance of severe symptoms such as tremors or speech difficulties. With the goal of recognizing and treating neurological diseases earlier, researchers are looking for new ways to image biological molecules that indicate disease progression before symptoms appear. One such candidate, and a known hallmark of Parkinson's disease, is the formation of clumps of alpha-synuclein protein, and, while this protein was identified more than 20 years ago, a reliable way to track alpha-synuclein aggregates in the brain has yet to be developed.

Now, a new study published in *Chemical Science* describes an innovative approach for identifying molecules that can help track the progression of Parkinson's disease. Conducted by researchers in the labs of E. James Petersson, Robert Mach, and Virginia Lee, this proof-of-concept study could change the paradigm for how researchers screen and test new molecules for studying a wide range of neurodegenerative diseases.

Studying these types of proteins aggregates requires new tracers, radioactive molecules that clinicians use to image tissues and organs, for positron emission tomography (PET). As a senior researcher in the field of PET tracer development, Mach and his group worked for several years with the Michael J. Fox Foundation to develop an alpha-synuclein tracer, but without data on the protein's structure they were unable to find candidates that were selective enough to be used as a diagnostic tool .

Then, with the first publication of alpha-synuclein's structure and an increase in tools available from the field of computational chemistry, Mach and Petersson started collaborating on developing an alpha-synuclein PET tracer. By combining their respective expertise in radiochemistry and protein engineering, they were able to confirm experimentally where on the alpha-synuclein protein potential tracer

molecules were able to bind, crucial information to help them discover and design molecules that would be specific to alpha-synuclein.

In their latest study, the researchers developed a high-throughput computational method, allowing them to screen millions of candidate molecules, to see which ones will bind to the known binding sites on alpha-synuclein. Building off a previously published method, their approach first identifies an "exemplar," a pseudo-molecule that fits perfectly into the binding site of alpha-synuclein. Then, that exemplar is compared to actual molecules that are commercially available to see which ones have a similar structure. The researchers then use other computer programs to help narrow down the list of candidates for testing in the lab.

To evaluate the performance of their screening method, the scientists identified a small subset of 20 promising candidates from the 7 million compounds that were screened and found that two had extremely high binding affinity to alpha-synuclein. The researchers also used mouse brain tissues provided by the Lee group to further validate this new method. The researchers were impressed, and pleasantly surprised, by their success rate, which they attribute to the specific nature of their search method. "There's certainly a bit of luck involved as well," Petersson adds, "Probably the biggest surprise is just how well it worked."

The idea of using the exemplar method to tackle this problem came to first author and Ph.D. graduate John "Jack" Ferrie while he was learning computational chemistry methods at the Institute for Protein Design at the University of Washington as part of a Parkinson's Foundation summer fellowship. "The summer fellowship is designed to train students in new methods that can be applied to Parkinson's disease research, and that's exactly what happened here," says Petersson. "The ideas that Jack came back with formed the basis of a big effort in both

my lab and Bob Mach's lab to identify PET tracers computationally."

Now, as part of a large multi-institutional grant, Petersson, Mach, Lee, and many other collaborators are poised to take the lessons learned from this finding to develop PET tracers for Parkinson's and other neurodegenerative diseases. "I really see this as being a game changer on how we do PET probe development," says Mach. "The significance is that we're able to screen millions of compounds within a very short period of time, and we're able to identify large numbers of compounds that will likely bind with high affinity to alpha-synuclein. We're also going to apply this same method to the development of other probes that are important but have presented challenges to the field."

By developing reliable high-throughput tools that use detailed knowledge of protein structure, the goal of future efforts is to find new tracer candidates and get them into the clinic as soon as they are ready for testing. "It is certainly accelerated compared to what's typical," says Petersson about the timelines of the grant. "This can be something that takes 10 to 15 years in industry, and we're trying to do it in about five."

Mach adds that this effort is a perfect example of "how things work here at Penn," with success made possible by collaborations between researchers with diverse and unique skillsets. "Penn is a great place because you have a lot of talented people who have a true spirit of collaboration, and that's what it takes to do science in this day and age," he says.

More information: John J. Ferrie et al. Identification of a nanomolar affinity α-synuclein fibril imaging probe by ultra-high throughput in silico screening, *Chemical Science* (2020). DOI: 10.1039/D0SC02159H

Provided by University of Pennsylvania