Stanley Krystek
Senior Principal Scientist
Bristol Myers-Squibb

Dr. Krystek received his M.S. & PhD. in Biochemistry from Albany Medical College in 1989. Dr. Krystek came to Bristol-Myers Squibb (BMS) in 1989 and has remained at BMS throughout his career. Dr. Krystek focused his efforts developing computational methods for protein modeling and drug discovery applying the methods to understanding protein-protein interactions for important therapeutic targets such as GPCRs, proteases, and NHRs. He is a recognized expert in protein engineering and design and he plays a key role in BMS protein biologics drug discovery programs. Dr. Krystek has published over 50 papers in the area of protein structure and modeling including application of QSAR methods to drug discovery, structure-based drug design and GPCR modeling. He is the co-inventor on over 20 patents.

Currently Dr. Krystek is Senior Principal Scientist in the department of Molecular Structure and Design where he leads a team that is focused on using in silico methods to support protein modeling and engineering of protein therapeutics. He is also member of the Scientific Advisory Board for Rider University.

We met with him to discuss the latest trends in computational drug development, industry challenges and the future of biologics. Read the full interview below.

For those who are unfamiliar with the concept of utilizing in-silico tools for drug discovery and drug development, where does the value lie in harnessing this approach and what do you think is driving the progress in the field most significantly?

I think the most important thing about the application of in silico tools for drug discovery and development is that computational methods for small molecules has gotten very mature. We have many learnings from the past 25/30 years where we know exactly how we can impact drug discovery and improve development time and cost. As we move to the biologics space, given this remains a newer area for us, I think we're still trying to determine which are the best methods to use and what are the properties we want to predict to effect faster outcomes.

The most important thing is clearly our ability to collect experimental data from which we can actually develop in silico models. There has been a huge explosion of this data, however access to the data may be limited as each company considers parts of the information proprietary– much like when the human genome was sequenced, the field of bioinformatics was established. To continue that analogy, we're in that same phase where we're looking to take the experimental information that's available on a therapeutic target and develop in silico rules or models that allow us to expand our prediction capabilities for biologics.

> "One of the biggest challenges is our ability to find a way of sharing data"

Further to the advances you've pointed to, there have been an number of interesting collaborations formed such as the biologics modelling and informatics (BMI) discussion group, of which you're a founding member. What are the drivers for the formation of this group?

One of the biggest challenges is our ability to find a way of sharing data. As such, one of the reasons we established the BMI as a discussion group, was so that we could bring together leaders from the bio-pharma industry across the world, and try and determine what our common needs are. What's really emerged is the willingness and the interest in sharing experimental data, to ensure there is enough data available to actually develop predictive in silico methodologies.

Whilst there's been a relatively strong uptake in computational technologies, this has been relatively slow thinking, specifically to biologic modelling, by comparison with the small molecule space. Is this the result of cultural barriers within pharma? What do you feel we need to do to combat and adapt this mindset?

If you look at the software providers, such as Chemical Computing Group, Schrodinger or Cyrus Bio, clearly the industry is supporting the need for protein property predictions and technology advancement. Certainly in the last year, I've seen an increase in the industry's interest in establishing in silico based rules for drug discovery and presumably, this will just follow into the development space.

However, the whole problem revolves around our ability to accurately predict the properties of proteins and other biologic therapeutics. So, with the small molecule space, we can use very rigorous methods to calculate

confirmations and properties of small molecules, and correlate those to specificity, affinity, stability and activity of the molecules. When you have a protein which is hundred times larger than a typical small molecule, our ability to calculate accurately those same properties of activity, affinity, specificity, stability, aggregation, solubility, viscosity, is much more difficult.

I think what we often do with current in silico methods is to predict trends rather than predict accurately a specific property – and I think that's why the uptake has been a little bit slower.

> “Over the next five years there'll be a huge revolution where we see techniques such as Cryo-EM and other methods aimed at studing how alterations in molecular structures affect biological function.”

With this said, where do you feel that we need to be investing our time and efforts over the next 5 years to really reap the benefits of computer aided design and development?

I think one of the first things that we need to do is to invest in accurate structure determination for protein therapeutics. There are some efforts being done here and again the BMI is a big proponent of this. We've sponsored seminars in this space and even at the CDD summit in 2016, we had a number of representatives give talks about the value and importance of structure as well as the novel features that you see when you can solve enough of these. With this said, we all need to invest our efforts to ensuring there are enough structures of antibodies and/or of other biologics, given property predictions are often dependant on structure function relationships.

The second investment needs to focus on the computational methods that we utilize to interpret those structures as well as the structural information we use to calculate the various properties, which are so important to manufacturability and developability. So, I think before we can invest in that we really need to make sure that we're confident in our ability to calculate structures or predict structures and then how to move that forward.

I think over the next five years there'll be a huge revolution where we see techniques such as Cryo-EM and other methods aimed at studing how alterations in molecular structures affect biological function.

Further to accepting my invitation to once again present in the meeting, I'm delighted you accepted the role of chairman for the 2nd Annual CDD for Biologics Summit. What are you most looking forward to at the upcoming meeting and what were the key reasons for taking this role?

What's most exciting to me is that I saw the success of the first conference last year. The meeting you produced in December 2016 was the first time that a bunch of like-minded scientists got together to actually discuss what our common needs and goals were.

Thinking back, this meeting was probably the nucleus for forming the Biologics Modelling and Informatics (BMI) discussion group. The discussions that emerged from the meeting were centred around challenges we all face being data sharing, standardisation of algorithms, standardisation of the types of properties, and how we should report all this information.

It's no surprise that so many experts and software vendors are interested in not just attending but also in speaking and sharing data to advance the field.

With this said, I think communication is what I like most about this meeting. Unlike other meetings I've been a part of, it has a format that allows experimentalists, protein engineers and computational scientists to interact with each other at a very high-level to understand how we can better invest into this area.

Thanks for your lovely comments. As I mentioned above your also going to be giving an keynote within the meting. Can you give us a preview of some of the key points which you'll be addressing?

Sure. One of the things that often gets overlooked when we think about developing therapeutic agents, in particular antibodies, is what really makes a good antibody. In my talk, I'm going to share insight about antigen design where my philosophy has always been “garbage-in-garbage-out”. I mean, if you generate antibodies using a non-specific or poor antigen you will not get the quality molecules that you want. As such, I'm going to describe how antigen design has an impact on the quality of the protein therapeutics that are produced. I'll also be reviewing everything from sequence property, structural property in antigen/epitope prediction and antigen design for immunization strategies.

> “The meeting you produced in December 2016 was the first time that a bunch of like-minded scientists got together to actually discuss what our common needs and goals were.”

A huge thank you to Stanley Krystek for taking the time to share his insights with us.

If you enjoyed reading about Stanley's experiences, there will also be an opportunity to meet him at the CDD for Biologics Summit (December 5-7, Boston).

For more information about the event, visit the website at www.cdd-biologics.com