Cambridge Healthtech Institute's

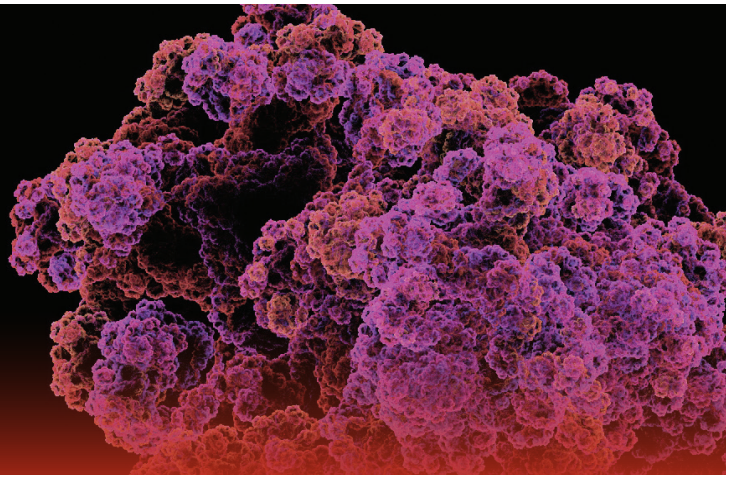
16th Annual

PEPTALK

THE PROTEIN SCIENCE WEEK

January 9-13, 2017 | San Diego, CA

Hilton San Diego Bayfront



Understanding Chemical Liabilities in Antibody Lead Selection

Shrikant Deshpande, Ph.D., Senior Director, Protein Chemistry, Biologics Discovery California, Bristol-Myers Squibb Co.

Cambridge Healthtech Institute recently spoke with Dr. Shrikant Deshpande of West-Ward Pharmaceuticals about his insights on characterization of biologic and where this field is headed in coming years. Dr. Deshpande is a keynote speaker at the **3rd Annual Characterization of Biotherapeutics taking place January 9-10 in San Diego, CA** where he will be delivering his talk on **"Understanding Chemical Liabilities in Antibody Lead Selection."** This conference is part of the **16th Annual PepTalk event** which runs from **January 9- 13, 2017 in San Diego, CA.**

SPEAKER Q&A

Q What are the most pressing issues in characterization of biologics?

Biopharmaceuticals are usually large molecules with a high structural complexity as compared to traditional small molecular weight pharmaceuticals. For example, therapeutic antibodies are multi domain proteins with several disulfides joining these domains. Several post translational modifications such as glycosylation, pyroglutamic acid formation, deamidation, methionine oxidation found during the cell culture and manufacturing processes increase the heterogeneity of these molecules. There is always a push from discovery to design superior molecules with better efficacy and lower toxicity with less or no emphasis on manufacturability and stability. The situation becomes more complicated when there is constant pressure to increase the product titer in the expression systems. These events may lead to unintended structural and post-translational consequences that might affect the biological outcome. The biggest challenge is to strike a balance between choosing an optimal molecule and manufacturability and be vigilant about the unintended consequences. With the advances in mass spectrometry and other protein biophysical characterization techniques, it is possible to identify and quantitate structural changes as well as post translational modifications. However, the trick is to employ these advanced techniques to identify the chemical liability issues in the discovery or very early stages of development so that the risk factors in the manufacturing and storage are understood early and appropriate mitigation strategies are put in place. In some cases, even changing the lead molecule could be one of the risk mitigation strategies if the issues are identified early enough.

Q Why is it important to understand and mitigate chemical liabilities?

Chemical liabilities can potentially modify the product characteristics. For example, a NG sequence in the CDR of an antibody could potentially be susceptible for deamidation followed by iso-asp formation thus altering the target binding structure and triggering biological consequences. A NG sequence in the Fc of an antibody could be a deamidation hot spot that could alter FcR binding characteristics leading to altered effector functions. Though there is deamidation in both scenarios, the mechanism of deamidation could be different and therefore, liability mitigation strategies to be applied will be different. In one case liability risk has to be mitigated by altering the CDR sequence while in the other, formulation strategy could work. So it is important recognize chemical liabilities, understand the mechanism of protein degradation pathways and design mechanism based derisking strategies...

Q Where is the field headed in coming years and what's revolutionizing antibody (or biologics) research?

My work is focused on Antibody discovery for cancer immunotherapy. So I can talk about what is exciting in this field. With the approval of two cancer immunotherapy drugs (both antibodies), biopharmaceutical research has exploded in search of new checkpoint inhibitors as well as immune stimulating targets. Clinical trials using biopharmaceutical combinations to combat and even eradicate cancer have been increasing exponentially. Finding a right combination(s) of immunotherapy drugs to cure cancer and improve the lives of the patients would be revolutionary and I feel it is certainly achievable in the next decade.

Q Why have you chosen to speak at 3rd Annual Characterization of Biotherapeutics track being held as part of PepTalk?

For the past several years, I have tried to bridge the gaps between discovery and development for biopharmaceuticals in general an antibody therapeutics in particular. In this regard, screening of hundreds of antibodies, profiling their sequences, carefully studying their characteristics and funneling top antibodies into the lead selection process and ultimately selecting a lead that could be transitioned into development is one of key interest. Understanding chemical liability risks, and de-risking these liabilities without compromising the required characteristics of the

SPEAKER BIOGRAPHY:

Shrikant Deshpande, Ph.D., *Senior Director, Protein Chemistry, Biologics Discovery California, Bristol-Myers Squibb Co.*

Shrikant Deshapnde received his Ph.D. from IIT Bombay and did his post-doctoral research in the area of radiolabeled monoclonal antibodies. His experience and interests include research in the area of protein/antibody therapeutics for autoimmune diseases and cancer immunotherapy. Currently, he works at BMS as Senior Director, Protein chemistry.

TO LEARN MORE ABOUT HIS PRESENTATION AND PEPTALK, VISIT: **CHI-PepTalk.com/ADC-bispecific-characterization**

antibodies (both CMC as well as biological) in the early stages of discovery is challenging but doable. We have done this exercise for many targets and for many lead selection processes. So peptalk meeting is a good forum for sharing the experience and generate further discussion on the role of chemical liabilities in discovery and development of Biologics.

Q What can audience expect from your presentation on Understanding Chemical Liabilities in Antibody Lead Selection?

Proteins are heterogeneous by nature. Chemical liabilities add to the complexity. Can we mitigate all the risks posed due to chemical liabilities? Probably not. But if try to understand the nature of these chemical liabilities in the context of CMC processes to be employed and intended use of the product (product profile) we might be able mitigate or lower the risks arising due to major liabilities paving the way to the development optimal if not ideal product.

Q What are you looking forward to at this meeting?

I am looking forward to exciting and cutting edge analytical methods for the characterization of biopharmaceuticals as well as discussions with industry and academic leaders on the current issues in biopharmaceutical discovery as well as develpment.