THE CHALLENGES OF PROTEIN ENGINEERING IN MONOCLONAL ANTIBODIES

VADIM KLYUSHNICHENKO, Vice President, Pharmaceutical Development & Quality, **CALIBR, A Division of TSRI**

Vadim Klyushnichenko, Ph.D. has served as Vice President of Pharmaceutical Development and Quality at Calibr, a division of The Scripps Research Institute since April 2016. He is responsible for process development, GMP manufacturing, quality assurance, CMO/CRO management, and the supply chain of the Calibr clinical product portfolio, which includes novel and reformulated small molecules, engineered peptides and proteins, and novel, switchable CAR-T cell platform to treat cancer. Dr.Klyushnichenko has over 20 years of experience in Bio/Pharmaceutical Development and Manufacturing. His drug delivery experience includes formulation of proteins, peptides and small molecules in micro-crystals, micro- and nano-particles, liposomes, degradable matrixes, as well as the development of controlled-release systems and devices for oral, injectable, implantable and pulmonary drug delivery. Vadim has developed his managerial responsibilities as VP of Drug Development at Paragon BioServices, Terapio Corporation, and Coldstream Laboratories Inc. Previously, he served as Principal/Senior Scientist at Wyeth/Pfizer, Baxter, Altus and Aventis/Sanofi. Vadim has received his B.S. in Physics from Moscow Institute of Physics and Technology (FizTech), Ph.D. in Chemistry from the Russian Academy of Sciences, and continued his postdoctoral research in Germany and Canada.

What are you working on in particular at the moment?

We are developing several drugs based on monoclonal antibodies. One of them is a bi-specific fragmented antibody (Fab) conjugated to a small molecule through an unnatural amino acid incorporated in the protein sequence. The drug is designed to treat the metastatic, castration resistant prostate cancer. This is a unique approach because the structure of the conjugate is similar to ADC, but the small molecule is not toxic. Instead, it has a high affinity to the specific protein expressed on the surface of prostate cancer cells. Another project is related to the switchable CAR-T cells, which has two units: CAR-T cells and Fab, which serves as a switch between a malignant cell and the modified T-cell. This "switchable" platform technology provides better control to address major limitations of current CAR-T cell approach, particularly related to the drug safety and efficacy. The third project is so-called fusion monoclonal antibody designed for the long acting therapeutic effect. It consists of the full-size monoclonal antibody (mAb) with the incorporated sequence of the therapeutic protein.

How do you see the large molecule field as it currently stands? And what are the major developments?

There is a lot of development in monoclonal antibodies, particularly related to the protein engineering: development of mini-bodies, nano-bodies, single chain variable fragments and proteins conjugated to small molecules. Another promising and fast-growing segment of the biopharmaceutical industry is gene and cell therapy, which requires the development of viral vectors. However, there is a lot of speculation regarding the overinflated cost of the projects completed by CMOs. While some companies invest heavily in the process development and manufacturing capabilities of viral vectors, the majority of clinical manufacturing services are based on traditional planar systems, which can provide enough material not only for extended clinical trials, but also for commercial manufacturing.

What are your biggest challenges in this area at the moment?

Considering the diversity and uniqueness of our projects, my biggest challenge is finding the appropriate CMOs, which can address very specific needs in protein engineering with high quality. Most CMOs assure their clients that they are capable of fulfilling any need, but further due diligence reveals their limitations. For this reason, our complex projects may involve up to five CMOs working in conjunction on drug substance development and manufacturing, production of intermediates, formulation, aseptic fill-finish and clinical supply chain. It's important to asses the strengths and weaknesses of each company to distribute the work most efficiently. To address these challenges, we have developed a thorough business and quality due diligence process and CMO selection criteria.

Could you provide an example of your challenges when it comes to finding the right CMO?

While the production of the therapeutic proteins through CMOs is a well-defined process, the development and GMP manufacturing of viral vectors and cell therapy products is still challenging from a technical, quality and business standpoint. The majority of academic or early stage development is supported by federal grants. If the price of the viral vector itself is greater than a million dollars, then the early development is ceased. The prices for some parts of viral vector development and manufacturing among different CMOs vary more than a tenfold. The major reason for that is the quality of the services, technical operations and business set up. This requires a thorough understanding of various analytical methods for the characterization of different products, manufacturing processes and controls, as well as the financial basis for their implementation. Frequently, the prices are driven by the lack of experience, line up of potential clients and future commercial demand. Meanwhile, the real clients are still in early clinical stage and the likelihood of their future commercial success is relatively low. Thus, it is important to find CMOs that have a good balance between technical expertise, quality and cost.

What is a particular issue for drugs that have a small patient population? Is it even more difficult to manufacture in that area?

Actually, the number of patients doesn't influence the complexity of drug development and manufacturing. It is still crucial to adhere to good manufacturing practices and to address the high quality of drug products even though they are intended for a smaller population. However, since the manufacturing batches are smaller, the cost of the final product increases. For example, the cost of so-called "orphan drugs" may exceed $300K per year. It is phenomenal that patients with rare diseases can finally get specialized medications, resulting in a significantly higher quality of life. However, the manufacturing companies should continue to strive to improve their manufacturing operations to reduce the cost of the "orphan drugs".

What is the one core thing when selecting a CMO that you would always look for?

The main factor for the selection of CMO is the quality. However, multiple parameters should be considered, such as technical capabilities and prior expertise with similar projects, analytical development and qualification approach, facility design and functionality, personnel experience, documentation and regulatory compliance. With that, the CMO quality should be in the balance with other factors such as the project cost and timeline.

Does location play a big part in selection?

The CMO location is not the major factor for us. The majority of drug development and manufacturing can be done remotely. We work with facilities in the US, EU, and Asia. While far away, India and China are developing rapidly and use state-of-the-art technology. At the same time, the complexity of our projects, deems it necessary to keep the internal technical, quality, and business expertise in order to be prepared for rapid changes.

What are you looking to get out of conferences like this?

The novel ideas in the presentations of each speaker are impressive. I appreciate the opportunity to learn more about new trends in formulation and drug delivery and network with leading pharmaceutical scientists. It is always a pleasure to network with passionate and brilliant people.