DEVELOPABILITY OF MABS

JENNIFER DREW, Investigator, **GlaxoSmithKine**

Jennifer has worked for GSK for over 10 years and in this time has gained experience working with a range of antibody formats including mAbs, dAbs, dAb fusions and mAb-dAbs. In the past 3 years her work has focused on developability and she has developed screens to assess the solubility of mAbs targeting high concentration formulations. Currently she is leading the in vitro translational work within Molecular Design and Engineering group to try to understand more about the in vivo suitability of mAbs e.g. are they likely to exhibit non-specific binding, unexpected binding to FcRn or low bioavailability. This work aims to further improve other developability screens at GSK.

Prior to our 2020 Proteins & Antibodies Congress, we sat down with Jennifer Drew from GlaxoSmithKline to discuss recent mAB progress, future opportunities in the area and the interesting work she is currently undertaking.

The antibodies market has seen a vast expansion over the last few years. In your opinion, what are the key factors driving its growth?

The flexibility of antibody formats means that there is a great diversity of indications that they can be used for. From providing targeting of toxins as part of ADCs and extending the half-life of other proteins in Fc-fusions, to providing bridging of several targets for example in Immuno-oncology applications and CAR-T cells, the limit is the imagination. In addition a wealth of knowledge has built up over the past decades allowing us to become better at discovering and manufacturing antibodies, with increased understanding of the importance for example of off-target effects that can be tested prior to drugs reaching patients and hence avoided. This, along with a much better understanding of target biology and therefore efficacy of antibodies has combined to drive growth.

What recurring challenges do you observe in the industry currently?

One of the current challenges is around the generation of Anti-Drug Antibodies (ADA) that can have an impact on safety through adverse reactions such as anaphylaxis through to premature drug clearance interfering with the Pharmacokinetic properties of a drug. Efforts are being made to reduce the likelihood of ADA generation through minimizing T cell epitopes. There are other challenges in the area of immune-oncology for example in understanding how to improve response rates and in manufacture of bispecific and tri-specifics and how to fine- tune antibody drug conjugate molecules with the right target / drug combinations.

What are your current research interests and how would our event help you achieve your 2020 goals?

The area of focus for me at the moment is developing new in vitro translational assays with the purpose of predicting unexpected clearance or in other words using in vitro techniques to determine in vivo suitability. I hope that the event will lead to discussion and learnings that will give me further insights into the techniques that can be used to predict in vivo suitability, increasing the diversity of assays that we have in place and thus increasing the understanding of the mechanisms of clearance and early prediction at the lead panel stage.

You are heavily involved in the developability of mABs. Why is it so important to study this area?

Developability covers a wide range of attributes that fit under the 3 pillars of Manufacturability, Safety and Pharmacology & Biological activity. For any new therapeutic candidate we need to answer questions such as : can it be made (at the right cost)? Is it stable? Can it be formulated for the intended route of administration? Is it safe for patients? Can it access the target tissue/organ at the required dose and during an adequate time window? Will it produce the intended biological activity and show sufficient effectiveness in patients? We are attempting to answer these types of questions at an earlier and earlier stage in the drug discovery process, which brings in the need for predictive assays. The more that we study the analytical techniques and assays that we use and improve them to be truly predictive , the better chance of success we have. Therefore, developability is important to allow us to assess the likelihood of being able to successfully develop a mAb, allowing us to select the candidates with the best chance of success to deliver medicines to the patient.

What do you think the future holds for mABs?

mAb formats are evolving to enable bispecific and trispecific spatial or temporal targeting of 2 or more targets at once, thus opening up treatment options for more patients as drugs using these approaches move through clinical trials. Currently intractable targets may well be reached through improvements in selection methods and the use of camelid and other formats . Use of other Ig types such as IgA and E may well emerge for Oncology indications. Oligoclonal mixtures of antibodies have been shown to have synergistic effects in come indications such as HIV, which could mean a different model for discovery and development of medicines for infection indications at least. There is an increasing body of work related to Fc engineering for tailoring the effector functions of antibodies impacting the mechanism of action. In addition modifications to tailor the half-life of antibodies, which impact the dosage interval and cost of goods, are being validated.

Jennifer will be speaking on the developability of mAbs at our 13th Annual Proteins & Antibodies Congress, 27 – 29 April 2020.