THE IMPACT OF BIPARATOPIC ANTIBODIES ON IMMUNO-ONCOLOGY

BONNIE HAMMER, Vice President of Biologics Development, **Invenra, Inc**

Bonnie J. Hammer, Ph.D. is the Vice President of Biologics Development at Invenra, Inc. headquartered in Madison, Wisconsin, USA. Invenra is a biotechnology company focused on the discovery and development of multispecific antibodies for immuno-oncology using their proprietary B-Body™ platform. Dr. Hammer holds a Ph.D. from the University of Oregon in Biochemistry and has over 20 years of experience in cell biology, disease modeling, and assay development for drug discovery. In her current role, her team focuses on high-throughput in-format screening of multi-specific antibodies in functional cell-based assays to rapidly identify the optimal combination of antibody epitopes, affinities, and geometries that lead to the preferred activity. Prior to joining Invenra, Dr. Hammer held research and development leadership roles in the Discovery Assays and Services business unit of Life Technologies.

Why do you think that biparatopic antibodies can have such an impact on immuno-oncology?

More broadly, I would say our company works on bispecific antibodies, and they can have different mechanisms of action than monospecific monoclonal antibodies. Three areas in particular are in immune cell redirecting antibodies, where one arm binds to an immune cell like a T cell or macrophage and the other binds to a tumor antigen - that can only be done with bispecific antibodies. The second area is when you want more specific targeting of a tumor cell, for instance; perhaps your tumor antigen is also expressed somewhere in normal tissue. If you have a second tumor antigen that is also expressed in the tumor but not in the same normal tissue, you can use a bispecific antibody to get more specific targeting of the tumor cell over the normal tissues. The third area is what I spoke about, i.e. biparatopic antibodies. A lot of immune cell receptors require clustering, and that clustering with a regular monospecific monoclonal antibody requires Fc engagement; with a biparatopic antibody, you can get clustering without requiring Fc engagement.

Could you explain a bit more about your company's approach to that?

Invenra's bispecific platform is called the B-body, and it looks like a standard human IgG1. The Fc domain uses a knob-into-hole mutation set in order to get the proper heavy chain - heavy chain pairing. One of the Fab-arms is just a wild type Fab-arm, and that can be a plug and play with antibodies coming from any discovery source. In the case of the other arm, we've done a CH1:Cl domain substitution with a domain from a different human antibody source, which really gives us an appropriate heavy chain - light chain pairing.

Are there any recurrent challenges you come across when you're doing this work?

I'd say one of the biggest challenges we talked about this morning in the roundtable discussions is the In Vivo models. When you're using bispecific antibodies, you have two different targets. For the *In Vivo* modeling you can use humanised mice, but not all the immune components are present in them. I can use human knock-in mice but if you're doing bispecifics, oftentimes you need at least two targets double knocked in, or sometimes you need both the target and the ligand. You might be talking about four different targets that are knocked in. Otherwise you need to have a surrogate molecule, and then surrogates have their own issues in that you need to match the epitopes and the affinities between the mouse and the human.

What are the top three takeaways from your presentation?

That biparatopic antibodies work extremely well for clustering antibodies. This is more broadly applicable to any receptors that required clustering for activity. Hopefully, I showed that our OX40 lead molecule has some advantages over the monoclonal antibodies that have thus far been through the clinic and that bispecific antibodies in general have a good future.