Special Seminar: Design principles for bispecific IgGs – opportunities and pitfalls of artificial disulfide bonds

Event Type: Special Seminar
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Date: Oct 24 2019 - 11:00am to 3:30pm
Location: 2129

ABSTRACT

Bispecific antibodies (bsAbs) are antibodies with two binding sites directed at different antigens, enabling therapeutic strategies not possible with conventional monoclonal antibodies (mAbs). Since bsAbs are regarded as promising therapeutic agents, several bsAbs design modalities have been evaluated, but as most of them are small recombinant fragments, their utility is limited. In a nutshell, the field prefers IgGs.

Two challenges should be met to make bsAbs IgGs; one is that each heavy chain will only pair with the heavy chain of the second specificity and that homodimerization will be prevented. The second is that each heavy chain will only pair with the light chain of its own specificity and not with the light chain of the second specificity. The first solution to the first criterion (knobs into holes, KIH) was presented in 1996 by a group from Genentech. Additional solutions were presented more recently. However, until recently, no solutions for the second criterion that make it possible to produce a bsAbs IgG by an expressing cell were suggested.
We present a solution for the second challenge - correct pairing of heavy and light chains of bispecific IgGs; an engineered disulfide bond between the antibodies’ variable domains that asymmetrically replaces the natural disulfide bond between CH1 and CL. Bispecific IgGs where the artificial disulfide bond is placed in the CH1-CL interface are also discussed. We show that our solution works for IgGs produced by our “Inclonals” technology for making full-size IgGs in *E. coli* as well as for IgGs secreted from Mammalian cells. We present A potential novel approach for precise evaluation of correct chain pairing by LC-MC-MS combined with chemical crosslinking. Examples will be provided for some of these bsAbs and future directions of the study will be discussed.

**Setup**

**IT Setup:** Projector

Laptop