



International Conference on
Animal & Dairy Sciences

July 23-24, 2013 Embassy Suites Las Vegas, NV, USA

Holy cow-reshaping bovine antibody diversity with disulfide-bonded ultralong CDR H3s

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Cows have limited genome encoded combinatorial diversity potential in their immune system, yet mount a robust antibody response. Cows have few V-regions but exceptionally long CDR H3 loops, however the mechanism for creating diversity is not understood. Crystal structures of two cow antibodies reveal that these CDR H3s form a very unusual architecture composed of a β -strand "stalk" that supports a structurally diverse, disulfide-bonded, "knob" domain. Deep sequencing revealed that ultralong CDR H3s contain a remarkable complexity of cysteines, suggesting that these disulfide-bonded mini-domains may arise during repertoire development. Sequence analysis indicates that diversity arises from somatic hypermutation of an ultralong DH with a severe codon bias towards mutation to cysteine. These unusual antibodies can be elicited to recognize defined antigens through the knob domain. Thus, the bovine immune system produces an antibody repertoire composed of CDR H3s of unprecedented length that fold into a diversity of mini-domains generated through combinations of somatically generated disulfides.

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