Transgenic Mouse Generates Human Single Domain Antibody VH Fragments

Crescendo Biologics announces the Crescendo Mouse using antibody fragment technology that allows the efficient generation of high-quality fully human single domain antibody V_H fragmentsfrom a transgenic mouse. V_H fragments are next-generation antibody-based therapeutic proteins that have applications beyond the scope of full length antibodies. They are the smallest antibody fragments that retain the ability to bind antigens specifically and with high affinity and, when generated in the Crescendo Mouse, human V_H have biophysical properties that make them highly attractive drug products. V_H fragments can be formulated for topical delivery, are highly amenable to modular engineering of bispecific and multivalent products, have superior tissue penetration characteristics, and are simple to manufacture in microbial systems.

Key to generation of V_H fragments in the mouse is Crescendo's proprietary triple knock out (TKO) background, which is completely devoid of all endogenous immunoglobulin chains, and therefore enables *in vivo* maturation of human V_H single domains uncontaminated by association with any light chains. B cell development within the Crescendo Mouse is driven from a construct introduced into the TKO background that combines human V- D- and J- genes, together with murine constant and regulatory regions, to generate heavy chain only antibodies. The power of the mouse immune system is consequently fully harnessed to drive B cell development and maturation, leading to a diverse repertoire of fully-human V_H domains with superior stability and solubility.

The Crescendo Mouse responds robustly to immunisation with target proteins and *in vivo* B cell maturation yields diverse human V_H domains, from all V_H families, which have also undergone somatic hypermutation. Because the antibody response following immunisation is entirely encompassed within the V_H domain, Crescendo has been able to develop a fully integrated discovery process utilising *in vitro* display to comprehensively mine and rapidly identify V_H drug candidates directly from immunised mice. Purified V_H fragments have been shown to bind immunogen with high affinity, exhibit very high thermostability and have excellent expression levels. These data indicate that B cell maturation in the Crescendo Mouse is driving selection and optimization of matured human V_H domains, with all of the properties that make them highly potent, drug quality antibody-based therapeutics.

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Links:
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