

The question, whether “fully human” mAbs such as derived from phage display libraries or transgenic mice are less immunogenic than humanized mAbs cannot be answered yet, because full immunogenicity data are available for just two human mAbs. An anti-tumor necrosis factor mAb, developed from phage-displayed human libraries induced antibody responses in 12% of patients - at the higher end of the incidence of anti-antibody responses of the humanized antibodies (Hwang, W. Y., et al. (2005). *Methods*, 36, 3-10).

Evaluation of the immunogenicity of the first registered human mAb generated by the transgenic approach demonstrated that mAb treatment resulted in the generation of antibodies in approximately 5.5% of treated cancer patients (Jakobovits, A., et al. (2007). *Nat. Biotechnol.* 25, 1134., Lofgren, J. A., et al. (2007). *J. Immunol.* 178, 7467).

A need therefore remains for a method and means for producing antibodies that are specific for their targets, but are less immunogenic. According to the invention the reduction of immunogenicity is at least partially achieved by providing a transgenic non-human mammal comprising, at least in its B cell lineage, a nucleic acid encoding at least an immunoglobulin light chain or heavy chain, wherein the heavy- or light chain encoding sequence is provided with a means that renders it resistant to DNA rearrangements and/or somatic hypermutations, preferably such a non-human animal is a rodent, more specifically a mouse. The nucleic acid preferably encodes a human, human-like or humanized immunoglobulin chain.

Summary

In one aspect, there is provided a method for the production of a transgenic mouse, comprising the step of introducing by site-specific recombination an expression cassette comprising a nucleic acid encoding a rearranged human VL region of a human immunoglobulin into the mouse germline, wherein the VL region is encoded by human germline V and

germline J segments, and, wherein the nucleic acid encoding said VL region is targeted to a locus that is resistant to silencing.

In yet another aspect, there is provided a transgenic mouse, comprising a nucleic acid encoding a rearranged VL region introduced into
5 its germline, wherein the VL region is encoded by human germline V and germline J segments, wherein the nucleic acid encoding said VL region is targeted to a locus that is resistant to silencing.

In yet another aspect, there is provided use of B cells obtained from the transgenic mouse as described herein after immunization of said
10 transgenic mouse with specific antigens as a source of VH regions.

Description

In the remainder of the specification mice are typically used as examples of the non-human mammals. The transgenic non-human mammalian hosts are capable of mounting an immune response to an
15 antigen, where the response produces antibodies having primate, particularly human, variable regions. Various transgenic hosts may be

Claims.

1. A method for the production of a transgenic mouse, comprising the step of introducing by site-specific recombination an expression cassette
5 comprising a nucleic acid encoding a rearranged human VL region of a human immunoglobulin into the mouse germline, wherein the VL region is encoded by human germline V and germline J segments, and, wherein the nucleic acid encoding said VL region is targeted to a locus that is resistant to silencing.
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2. The method of claim 1, wherein the expression cassette further encodes a murine light chain constant region.
3. The method of any of claims 1 or 2, wherein the nucleic acid encoding
15 said VL region is targeted to the mouse Ig kappa or lambda light chain locus so as to functionally inactivate the endogenous locus.
4. The method of any of claims 1 or 2, wherein the nucleic acid encoding said VL region is targeted to the Rosa locus.
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5. The method of any of claims 1 to 4, wherein the mouse is capable of producing antibodies harboring the VL region.
6. The method of any of claims 1 to 5, wherein the nucleic acid encoding said
25 VL region is introduced into pronuclei of fertilized mouse oocytes or embryonic stem cells.
7. A transgenic mouse, comprising a nucleic acid encoding a rearranged VL region introduced into its germline, wherein the VL region is encoded by
30 human germline V and germline J segments, wherein the nucleic acid encoding said VL region is targeted to a locus that is resistant to silencing.
8. The transgenic mouse of claim 7 wherein the mouse further comprises a murine light chain constant region.

9. The transgenic mouse of any of claims 7 or 8, wherein the nucleic acid encoding said VL region is targeted to the mouse Ig kappa or lambda light chain locus so as to functionally inactivate the endogenous locus.

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10. The transgenic mouse of any of claims 7 or 8, wherein the nucleic acid encoding said VL region is targeted to the Rosa locus.

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11. Use of B cells obtained from the transgenic mouse of any of claims 7 to 10 after immunization of said transgenic mouse with specific antigens as a source of VH regions.

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12. The use of claim 11, wherein the VH regions are obtained by constructing cDNA libraries or by PCR amplification using primers for human VH regions.