Molecular Insights into Fully Human and Humanized Monoclonal Antibodies

What are the Differences and Should Dermatologists Care?

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ABSTRACT

In recent years, a large number of therapeutic monoclonal antibodies have come to market to treat a variety of conditions including patients with immune-mediated chronic inflammation. Distinguishing the relative clinical efficacy and safety profiles of one monoclonal antibody relative to another can be difficult and complex due to different clinical designs and paucity of head-to-head comparator studies. One distinguishing feature in interpreting clinical trial data by dermatologists may begin by determining whether a monoclonal antibody is fully human or humanized, which can be discerned by the generic name of the drug. Herein, this commentary highlights the distinctions and similarities of fully human and humanized monoclonal antibodies in their nomenclature, engineering, and clinical profiles. While there are a number of differences between these types of monoclonal antibodies, current evidence indicates that this designation does not impart any measurable impact on overall clinical efficacy and safety profiles of a given drug. Based on molecular insights provided in this commentary, it is clear that each monoclonal antibody, irrespective of being fully human or humanized, should be individually assessed for its clinical impact regarding safety and efficacy. Going beyond the type of generic name ascribed to a monoclonal antibody will be an ever-increasing theme for dermatologists as more therapeutic monoclonal antibodies emerge to potentially treat a wider scope of diseases with cutaneous manifestations. (*J Clin Aesthet Dermatol.* 2016;9(7):13–15.)

Like naming your child, the naming of a monoclonal antibody (mAb) has important and lasting implications that can generate different impressions in the absence of context. With regard to a person's name, we potentially seek to discern more about the individual. Similarly, a clinician considering prescribing a "biologic" may ask: What can I learn from the generic name of this drug that is clinically meaningful in the context of my practice? The purpose of this commentary is three-fold: 1) review the process and criteria for naming mAbs produced by recombinant biotechnology; 2) provide scientific insights into the design and engineering principles leading to creation of mAbs-emphasizing distinctions and similarities between fully human and humanized mAbs; and 3) highlight potential engineering that goes beyond initial mAb design, which can contribute to improved structural characteristics that may translate into better immunological interventions. For all these objectives, the emphasis is to provide a useful clinical context so healthcare professionals can better appreciate the meaning and significance of the name attached to a drug that is being considered for the treatment of their patients.

THE NAME GAME—AN AMBIGUOUS PROPOSITION

While parents can name their child, pharmaceutical companies developing mAbs today cannot provide the generic name to their therapeutic protein. Rather, the assignment of antibody international nonproprietary names (INN) is determined by the World Health

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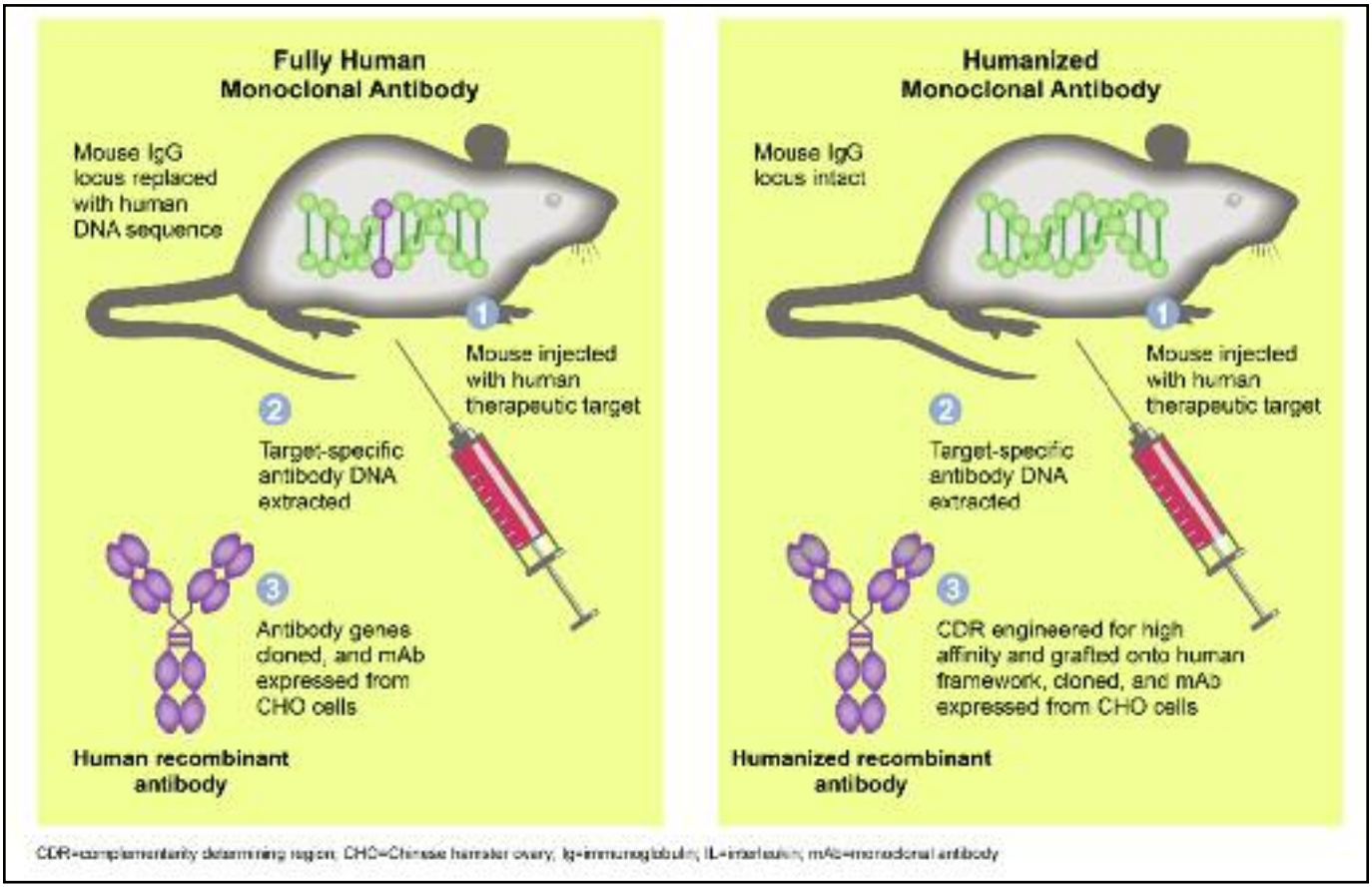

Figure 1. Production of both fully human and humanized mAbs begin in mice and end with hamster cells. Ironically, the multi-step process in generating fully human (left panel) and humanized (right panel) mAbs has little to do with actual human cells. Comparing both panels reveals similarities and differences in producing fully human and humanized mAbs. Note for producing fully human mAbs, the mouse genome is modified by the insertion of the human immunoglobulin locus. In contrast, humanized mAbs are generated in mice with an unmodified genome. In step 1 in both processes, mice are injected with the intended human therapeutic target (e.g., a recombinant protein). In step 2 following the subsequent immune response of the mouse to the human antigen, target specific antibody related DNA was extracted. For humanized mAbs, the sequences defining the hypervariable region (also known as the complementarity determining region [CDR]) are grafted onto a human antibody framework, cloned and engineered for high affinity. In step 3 in both processes, the cloned target specific antibody DNA is expressed as a mAb using Chinese hamster ovary (CHO) cells.

Organization (WHO), which designates the mAb as chimeric (-xi-), chimeric/humanized (-xizu-), humanized (-zu-), or fully human (-u-).[1] Under current INN guidelines, the designation of a generic name is not dependent on the bioengineering methodology leading to the creation of a given mAb.[1,2] Rather, the assignment of a mAb to a specific designation is dependent on the variable region of the immunoglobulin (i.e., the site providing specificity and affinity for an antibody).[1,2] Interestingly, threshold or cut-off values for defining fully human and humanized mAbs are more relative than absolute. It is the overall sequence of the variable region that is considered and then judged to more closely resemble human sequences (i.e., fully human and humanized mAbs) or non-human sequences (i.e., chimeric mAbs). Attempting to keep pace with and understand the process by which a therapeutic protein is named by the WHO and its revisions in criteria has been likened to "aiming for a rapidly moving target" due to the speed of technological advances in the design and engineering of mAbs.[2] Experts have identified inconsistences within the definitions and recommended a new system to avoid confusion for both researchers and clinicians prescribing therapeutic mAbs. There is a need to re-examine the definition of what constitutes a fully human antibody and what differentiates it from a humanized antibody. This is important, as receiving a designation as either fully human or humanized can have unintended consequences such as the notion that there is greater or lesser potential for clinical efficacy. In the following sections, distinguishing the engineering of fully human and humanized mAbs is emphasized as well as highlighting the potential impact these processes have on clinical efficacy.

MAKING A BIOLOGIC—BEING FULLY HUMAN RESIDES IN THE EYE OF BEHOLDER

When one initially hears the terms fully human or humanized mAbs, it can be surprising how little the methodology involved in making therapeutic mAbs actually involves humans. Whereas the process of generating fully human mAb can start either with phage display technology or animal immunizations, the process of generating humanized mAb always starts with animal immunizations typically utilizing mice (Figure 1). When mice are utilized, they are injected with the designated therapeutic target (e.g., protein), specific antibodies to the target are identified, and Chinese hamster ovary (CHO) cells are used to produce the mAbs. The distinction is that fully human mAbs can be developed in transgenic mice that have been genetically engineered with the human immunoglobulin locus while humanized mAbs are initially generated in wild type mice with a native genome bearing the mouse immunoglobulin locus. Portions of the initial antibody produced conferring specificity and affinity (mouse derived) are then grafted onto a human antibody sequence utilizing molecular engineering technology to generate a humanized mAb. This can result in mAbs that, in total, have high human amino acid (AA) sequence homology, with differences limited to complementarity determining regions (CDRs) within the variable region of the antibody (Figure 1). While humanized mAbs can be specifically engineered to have fully human frameworks with no mutations from germline in these areas,[3] antibodies from transgenic mice can have mutations which have been introduced by the mouse somatic mutation machinery.[4]

The aforementioned changes in the AA sequence homology of either fully human or humanized mAb can contribute to the development of anti-drug antibodies (ADAs), thereby potentially limiting clinical efficacy.[5] For example, dermatologists are aware that fully human mAbs can provoke neutralizing ADAs, which reduce clinical efficacy.[5,6] Thus the distinction between fully human and humanized mAbs has no generalizable impact on the development of ADAs based on nomenclature.[7,8] Rather, a number of intrinsic and extrinsic factors, including but not limited to the AA sequence of a mAb, are involved in the development of ADAs for a given therapeutic mAb.[5,7]

LOOKING BEYOND FULLY HUMAN AND HUMANIZED NOMENCLATURE TOWARD CLINICAL RESPONSES

Regardless of whether the mAb is fully human or humanized, further molecular engineering focused on the variable regions of a mAb may impart superior biophysical and biochemical properties such as higher affinity.[9] Furthermore, molecular engineering of a therapeutic mAb is not limited to enhanced affinity, but can also be directed toward other functional properties, such as improving stability and reducing immunogenicity.[7,10,11]

CONCLUSION

Clinicians are keenly interested in the efficacy and safety profiles of mAbs, as well as the tendency for development of ADAs that may impact safety and efficacy. While all these factors are dependent on complex cellular and molecular interactions beyond the scope of this commentary, it is clear nomenclature alone should not be an influence in the selection of a suitable biologic. Each mAb should be considered individually based on its risk-benefit profile and molecular insights that go beyond the naming of a mAb such as fully human and humanized.

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