

Intellectual Property Protection of MABs

With the large number of monoclonal antibody (MAB) therapeutics being developed, often against identical targets, obtaining strong intellectual property (IP) protection for antibodies has become a challenge. Increasingly, the use of epitope mapping has become necessary for demonstrating the patentability of therapeutic antibodies over prior art during the writing, prosecution, and litigation of patents. For example *In re Tzipori*, Fed. Cir. 2008 and *In re Alonso*, Fed. Cir. 2008, claims were rejected because the applicants did not sufficiently demonstrate how the claimed antibodies differed from prior art antibodies. In these cases, the courts stated that epitope characterization would have helped to make these critical distinctions. Epitope data not only strengthens novelty and patentability of an antibody but has also been successfully used to support broad antibody claims that have been granted by the USPTO. For example, a recently granted U.S. Patent (No. 6,787,637) generically defines a pharmaceutical composition comprising an antibody that binds a *specific* epitope, implying the ability to exclude others from targeting this same epitope with any other antibody. Finally, epitope data may be critical in supporting freedom-to-operate by providing a basis for non-infringement or invalidity of a third party patent.

Shotgun Mutagenesis Mapping

Shotgun Mutagenesis is an epitope mapping technique that uses a proprietary high throughput cellular expression technology for the analysis of mutated target proteins. Each amino acid of a target protein is individually mutated, and libraries of these mutants are expressed and assayed (Figure 1). Immunofluorescence is used to determine the reactivity of each MAb with each mutant clone, making it possible to identify every amino acid critical to the epitope. Shotgun Mutagenesis employs the use of functional proteins expressed in eukaryotic cells. Challenging protein targets such as

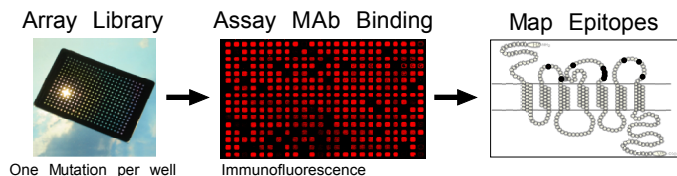


Figure 1. Shotgun Mutagenesis Mapping of MAB Epitopes. To map epitopes, the immunoreactivity of each MAb is tested against a library of protein mutants arrayed in 384-well microplates. Fluorescence intensity in each well is quantified to determine the reactivity of each MAb with each mutant clone. Critical residues identified can then be mapped.

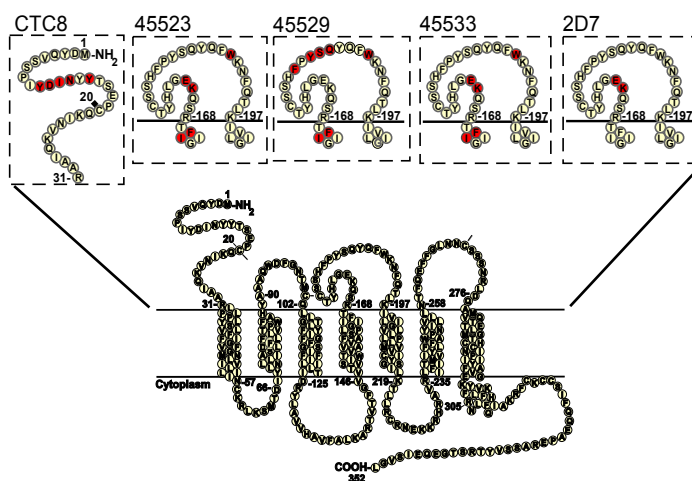


Figure 2. Epitope Mapping of a GPCR. The epitopes of five CCR5 MABs identified using Shotgun Mutagenesis Mapping are shown, shaded in red. All the epitopes except that of CTC8 require the native conformation of the protein.

membrane proteins, protein oligomers, or proteins with post-translational modifications are therefore readily mapped, without the need for purified forms of the protein.

Epitope Mapping by Shotgun Mutagenesis

Shotgun Mutagenesis Mapping can be used to show that the binding of different MABs to the same protein region can comprise distinct intellectual property. For example, Shotgun Mutagenesis Mapping was used to map the binding epitopes of five commercially available MABs on the chemokine receptor CCR5 (Figure 2). While a low-resolution technique such as competitive binding would only distinguish between vastly different epitopes, such as those of MABs CTC8 and 2D7, Shotgun Mutagenesis Mapping can effectively differentiate the epitopes of MABs 2D7, 45523, and 45529 that all bind the same region of the protein but that make contact with different individual amino acids. Therefore, Shotgun Mutagenesis Mapping could potentially be used to demonstrate the patentability of an antibody such as 45529 over a prior art antibody such as 2D7. Conversely, Shotgun Mutagenesis Mapping would be able to show that the epitopes for MABs 45523 and 45533 are identical, potentially protecting the antibody with first patent rights against infringement.

Contact Us

Shotgun Mutagenesis Mapping analyses of protein interactions are provided to customers on a fee-for-service basis, which includes customized Shotgun Mutagenesis Mapping of user-specified genes, data collection, and structural analyses. For more information contact us at:

215.966.6061

info@integralmolecular.com

www.integralmolecular.com