Molecular and Structural Properties of Three Autoimmune IgG Monoclonal Antibodies to Histone H2B* 

Received for publication, December 9, 1999, and in revised form, February 8, 2000

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In systemic autoimmune diseases such as lupus the immune system produces autoantibodies to nuclear antigens including DNA and histone molecules. In the present study, we describe three monoclonal IgG antibodies that have been obtained from lupus-prone MRL/lpr mice. These three antibodies react with the amino terminus of histone H2B, a region of the molecule that is accessible in chromatin. Using a series of overlapping H2B synthetic peptides and structural analogues, we have mapped the different epitopes recognized by these antibodies. We have also sequenced the combining sites (variable regions) of the antibodies and modeled their interactions with the corresponding epitopes. Overall, the data suggest that the mechanisms of interaction with antigen are different for each of the three antibodies, even though they all react with the amino-terminal domain of the histone H2B molecule. The results also suggest that the binding between these antibodies and histone H2B is different from that between most antibodies and conventional protein antigens since the heavy chain complementarity-determining region 3 appears to play only a limited role in the three antibodies tested. The study of the interaction between self-antigens and spontaneously occurring autoantibodies may help us elucidate the mechanisms driving the expansion of self-reactive lymphocytes.

* This work was supported by National Institutes of Health Grant AI-26665 (to M. M.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

The nucleotide sequence(s) reported in this paper has been submitted to the GenBank™/EBI Data Bank with accession number(s) AF143907, AF143908, AF143909, AF143910.

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§ The abbreviations used are: SLE, systemic lupus erythematosus; CDR, complementarity-determining region; ELISA, enzyme-linked immunosorbent assay; HPLC, high performance liquid chromatography; mAb, monoclonal antibody; PBS, phosphate-buffered saline; PBS-T, PBS containing 0.05% Tween; V, variable; Fmoc, N-(9-fluorenly)methoxycarbonyl.
Autoantibodies to Histone H2B

Table I
Peptides tested in this study

| Residue | Peptide | Peptide | Peptide |
|---------|---------|---------|---------|
| 1–6 (C) | P E P A K S (C) | 1–13 (C) | P E P A K S A P A P K K G (C) |
| 1–20 | P E P A K S A P A P K K G S K K A V T K | 1–20 (A1) | A E P E A K S A P A P K K G S K K A V T K |
| 1–20 (A5) | P E P A K S A P A P K K G S K K A V T K | 1–20 (A11) | P E P A K S A P A P K K G S K K A V T K |
| 1–25 | P E P A K S A P A P K K G S K K A V T K A Q K K D | 6–18 (C) | S A P A P K K G S K K A V (C) |
| 6–18 (C) | S A P A P K K G S K K A V (C) | 6–18 (C) blocked | Ac–S A P A P K K G S K K A A A A (C) –NH₂ |
| R1 (C) blocked | Ac–A A P K K G S K K A A A A (C) –NH₂ | R2 (C) blocked | Ac–A A P K K G S K K A A A A (C) –NH₂ |
| R3 (C) blocked | Ac–A P A E K K G S K K A A A A (C) –NH₂ | 13–18 (C) | G S K K A V (C) |
| 44–67 (SmD1) | K M T L K N R E P V Q L E T S I R G N N I R Y |

Table II
Direct ELISA reactivity of anti-H2B mAbs with histone H2B peptides

| mAb | Peptide 1–25 | Peptide 1–13 | Peptide 6–18 |
|-----|-------------|-------------|-------------|
| PR1–1 | 2.80 | 1.70 | 0.10 |
| LG2–2 | 2.80 | >3 | 0.30 |
| LG11–2 | 0.15 | >3 |

(A) and 0.08% trifluoroacetic acid in 80% acetonitrile, 20% water (B) at a flow rate of 6 ml/min with UV detection at 220 nm. The homogeneity of each peptide was assessed by analytical HPLC on a Beckman instrument with a nucleosil C18, 5-μm column (4.6 × 150 mm) using a linear gradient of 0.1% trifluoroacetic acid in water and acetonitrile containing 0.08% trifluoroacetic acid at a flow rate of 1.2 ml/min. Peptide identity was established by mass spectrometry using a protein time-of-flight apparatus (Bruker Spectrastion, Wissembourg, France). Synthesis of control peptide 44–67 of the SmD1 protein was described previously (18). Peptide 1–13 C was conjugated to ovalbumin using m-maleimido-benzoyl N-hydroxysuccinimide ester.

ELISA—The indirect ELISA procedure used to measure the binding of mAbs to nucleosome was as described previously (15) using microtiter plates (Falcon, Oxnard, CA; catalog number 3912) coated overnight with 50–400 ng/ml mononucleosomes in phosphate-buffered saline (PBS) pH7.4. To study mAb binding to H2B synthetic peptides, ELISA plates were coated overnight at 37 °C with each peptide diluted in 0.05 M carbonate buffer, pH 9.6. In each assay, mAbs were also tested in a noncoated well incubated with coating buffer as a control. Saturation of plates was obtained by adding PBS containing 0.05% Tween (PBS-T) and 0.4% bovine serum albumin. The subsequent steps of the test were performed as described previously (12) using mAbs diluted in PBS-T, 0.4% bovine serum albumin and rabbit anti-mouse IgG conjugated to horseradish peroxidase diluted 1:5000 in PBS-T. The final reaction was visualized by addition of 3,3′,5,5′-tetramethyl benzidine in the presence of H₂O₂. Inhibition experiments were performed as described previously (12) using peptide 1–25 H2B directly coated on the plastic at the appropriate concentration (0.1, 0.125, or 0.4 μg/ml), and the mAbs were incubated for 1 h at 37 °C and 1 h at 4 °C with the various competitor peptides (maximum peptide concentration tested in the fluid phase, 10 μg/ml). The reaction was revealed as described above. IC₅₀ values are defined as the amount (expressed in μg/ml) of competitor peptide necessary to inhibit the maximal antibody binding by 50%.

Variable Region Messenger RNA Sequencing—Poly(A)⁺ RNA was isolated from hybridoma cells using oligo(dT)-cellulose according to a previously described method (19). The variable region nucleotide sequences were determined by dyeodeoxy sequencing as previously reported (20–22). The nucleic acid sequences were compared with immunoglobulin sequences in the GenBank database (23). The variable region sequences were assigned to known gene families or germline genes by comparison with previously published sequences.

Modeling—All molecular modeling was performed on either a Silicon Graphics Personal IRIS 4D/25 or a Silicon Graphics Indigo2 workstation. Initial models were constructed using XAbgen, a suite of programs for homology-based antibody model generation (24). A model of the antigen-binding site for each antibody, formed by the six complementarity-determining region (CDR) loops, was constructed using the heavy and light chain variable region sequences for each antibody. The output of the XAbgen program, a model of the antigen-binding site in Protein Data Bank format, was used as the initial starting point for all further modeling.

Refinement of all molecular models was performed using the DREIDING II force field and biograf software (BIOSYM/Molecular Simulations, San Diego CA). The initial step in the refinement process involved minimizing the energy of the entire structure to convergence. After this, each structure was subjected to molecular dynamics calculations (200 ps), during which time only the atoms within the 6 CDR loops were permitted to move, while the motion of all the other atoms in the model was maintained constant. The energy of the entire structure was then refined by molecular dynamics calculations.

Thus, the peptide conformation within the antigen-antibody complex was predicted to move, while the motion of all other atoms within the structure were maintained constant; 3) the energy of the entire complex was minimized to convergence; 2) the molecular dynamics calculations (100 ps) were performed, during which time only the atoms of the 6 CDR loops, and those of the peptide antigen were permitted to move, while the motion of all other atoms within the structure were maintained constant; 3) the energy of the entire complex was then refined by molecular dynamics calculations; 4) the atomic positions of the peptide antigen and of the six CDR loops on each antibody were used as the starting point for all further modeling. The final step in our modeling procedure involved docking each peptide into the proposed binding site of the relevant antibody. Refinement of each antigen-antibody complex included the following. 1) The energy of the entire complex was minimized to convergence; 2) the molecular dynamics calculations (100 ps) were performed, during which time only the atoms of the 6 CDR loops, and those of the peptide antigen were permitted to move, while the motion of all other atoms within the structure were maintained constant; 3) the energy of the entire complex was then refined by molecular dynamics calculations; 4) the atomic positions of the peptide antigen and of the six CDR loops on each antibody were used as the starting point for all further modeling. The final step in our modeling procedure involved docking each peptide into the proposed binding site of the relevant antibody. Refinement of each antigen-antibody complex included the following. 1) The energy of the entire complex was minimized to convergence; 2) the molecular dynamics calculations (100 ps) were performed, during which time only the atoms of the 6 CDR loops, and those of the peptide antigen were permitted to move, while the motion of all other atoms within the structure were maintained constant; 3) the energy of the entire complex was then refined by molecular dynamics calculations; 4) the atomic positions of the peptide antigen and of the six CDR loops on each antibody were used as the starting point for all further modeling. The final step in our modeling procedure involved docking each peptide into the proposed binding site of the relevant antibody. Refinement of each antigen-antibody complex included the following. 1) The energy of the entire complex was minimized to convergence; 2) the molecular dynamics calculations (100 ps) were performed, during which time only the atoms of the 6 CDR loops, and those of the peptide antigen were permitted to move, while the motion of all other atoms within the structure were maintained constant; 3) the energy of the entire complex was then refined by molecular dynamics calculations; 4) the atomic positions of the peptide antigen and of the six CDR loops on each antibody were used as the starting point for all further modeling. The final step in our modeling procedure involved docking each peptide into the proposed binding site of the relevant antibody. Refinement of each antigen-antibody complex included the following. 1) The energy of the entire complex was minimized to convergence; 2) the molecular dynamics calculations (100 ps) were performed, during which time only the atoms of the 6 CDR loops, and those of the peptide antigen were permitted to move, while the motion of all other atoms within the structure were maintained constant; 3) the energy of the entire complex was then refined by molecular dynamics calculations; 4) the atomic positions of the peptide antigen and of the six CDR loops on each antibody were used as the starting point for all further modeling. The final step in our modeling procedure involved docking each peptide into the proposed binding site of the relevant antibody. Refinement of each antigen-antibody complex included the following. 1) The energy of the entire complex was minimized to convergence; 2) the molecular dynamics calculations (100 ps) were performed, during which time only the atoms of the 6 CDR loops, and those of the peptide antigen were permitted to move, while the motion of all other atoms within the structure were maintained constant; 3) the energy of the entire complex was then refined by molecular dynamics calculations; 4) the atomic positions of the peptide antigen and of the six CDR loops on each antibody were used as the starting point for all further modeling.

RESULTS AND DISCUSSION

In preliminary experiments (data not shown), we determined that the three mAbs described in this study (PR1–1, LG2–2, and LG11–2) specifically react with histone H2B but not with the other core histone molecules (H2A, H3, and H4) nor with DNA. Direct ELISA tests with overlapping peptides encompassing the whole H2B molecule indicated that all three mAbs recognized epitopes in the amino-terminal peptide 1–25 (data not shown). We therefore further characterized the reactivity of these mAbs against the histone H2B amino terminus. mAbs PR1–1 and LG2–2 strongly reacted with the amino-terminal peptide 1–13 but not with peptide 6–18. In contrast, mAb...
LG11–2 did not bind peptide 1–13 but strongly reacted with peptide 6–18 (Table II). We then tested the ability of various H2B amino-terminal peptides in solution to inhibit the interaction between the three mAbs and peptide 1–25 immobilized on the ELISA plate. As shown in Table III, the binding of PR1–1 mAb to peptide 1–25 was inhibited by peptides 1–25, 1–20, and 1–13 but not at all by peptides 1–6, 6–18, and 13–18, indicating thus that residues 1–13 are required for antibody recognition and that residues surrounding the serine residue at position 6 (Ser6) are important. Like PR1–1, LG2–2 binding was strongly inhibited by peptides 1–25, 1–20, and 1–13 but moderately by peptide 1–6 and not at all by peptides 6–18 and 13–18, indicating that residues 1–6 (with a few residues in the segment 7–13) constitute most of the epitope recognized by this mAb. Similar experiments were performed with LG11–2 (Table III). The binding of this antibody to peptide 1–25 was inhibited by peptides 1–25, 1–20, and 1–13 but not at all by peptides 1–6, 6–18, and 13–18, therefore confirming that the central segment of the 1–25 peptide (residues 6–18) contains the major part of the LG11–2 epitope. No reaction was observed with any of these three antibodies against the unrelated control peptide 44–67 of SmD1 (Table III). The epitopes recognized by the anti-H2B mAbs in our study are present on “native” structures, since all three mAbs react with purified calf thymus mononucleosomes when tested by ELISA (Table IV). These determinants are also accessible in chromatin, since the mAbs reacted with HEP-2 nuclei by immunofluorescence staining (not shown).

The H2B amino terminus is characterized by the presence of several positively charged lysine residues that are probably important for interaction with DNA in the nucleosome. We have therefore evaluated the role of two of these residues, Lys5 and Lys11, by replacing them with alanine side chains in mutant 1–20 peptides. We also tested the importance of the first proline residue (Pro1) by similarly replacing it with an alanine. The results of the antibody inhibition binding assays to these modified peptides are listed in Table III. With respect to the two mAbs specific for peptide 1–13, the binding of PR1–1 is totally abolished when Pro1 is substituted with Ala1 and moderately affected when Lys11 is replaced with an alanine residue, whereas the Lys to Ala substitution has no effect on PR1–1 binding. As with PR1–1, LG2–2 reactivity is abolished by the Pro to Ala substitution and only moderately affected by the Lys to Ala replacement. In contrast with PR1–1, LG2–2 binding is only partially decreased by the Lys to Ala replacement. Previous results indicated that LG11–2 is specific for a determinant located between residues 6 and 18, and as expected, alanine substitution at position 1 (Pro1 to Ala1) does not affect binding. The Lys to Ala5 substitution reduces LG11–2 binding only slightly, whereas reactivity is totally abolished by the Lys to Ala5 substitution.

We further characterized the reactivity of LG11–2 mAb (which reacts with residues located within the segment 6–18 of histone H2B) using various analogues of the parent peptide 6–18 (Table I). These peptide analogues were acetylated at their NH2 termini and carboxamidated at their COOH termini, and three of them (named R1, R2, and R3) also included sequence alterations from the original 6–18 sequence. Blocked peptides can assume a three-dimensional conformation different from conventional peptides that may result in alteration of antibody recognition (27, 28). The results of these binding studies are shown in Table V. As expected from the results described earlier in this paper, neither PR1–1 nor LG11–2 reacted with any of the 6–18 analogs, since both antibodies require residues 1–6 for binding. In contrast, LG11–2, which reacts with peptide 6–18, also recognized the blocked 6–18 peptide (Table V). However, LG11–2 did not bind to any of the analogue peptides, R1, R2, or R3 (Table V). Of these three analogues, R1 is the closest to the original sequence since the only differences between R1 and 6–18 occur at the NH2 and COOH extremities, whereas the core sequence APKKGSKKKA (residues 9–17) is identical in both peptides (Table I). The lack of binding of LG11–2 to this analogue suggests that the terminal residues of the 6–18 peptide may be involved in direct contact with the LG11–2 binding site or that some of these residues (e.g. Pro6, which was replaced in R1 by an acetylated alanine) play a critical role in the overall conformation of the epitope.
We then examined the heavy and light chain variable (V) region sequences of the three anti-H2B mAbs. The sequences of these V regions are available from GenBank/EMBL under accession numbers X67621, X67624, AF143907, AF143908, AF143909, and AF143910. To our knowledge, these are the only anti-H2B antibody variable region sequences to have been reported. The V, D, and J gene segment usage of our mAbs is summarized in Table VI, and the amino acid sequences of the CDRs are listed in Table VII. The variable regions of these mAbs are encoded by different D, JH, VK, and Jκ gene segments, and although the J558 VH gene family is used by all three mAbs, they utilize three different germine VH genes. Therefore, even though all three mAbs recognize determinants located in the amino terminus of histone H2B, they use different genetic elements to create their combining sites. To help us understand the interactions between these three mAbs and the H2B amino terminus, we modeled the structures of the three antibody-antigen complexes. Despite the uncertainties associated with these computational procedures, the predicted structures are a valuable aid, as they can provide a possible explanation for the binding interactions that have been experimentally determined. The structural elements used to generate the anti-H2B V region models are listed in Table VIII, and the results of these modeling studies are depicted in Fig. 1.

In the following descriptions of these interactions, the variable region residues are numbered on the line with the residue abbreviations according to the Kabat nomenclature (29), and the H2B peptide residues are numbered in superscript characters (see Table I for the H2B sequence). Both PR1–1 and LG2–2 react with the peptide 1–13 of H2B. For PR1–1 (Fig. 1, A and B), the heavy chain interactions involve Tyr-27 (located just outside of CDR1) with Pro3, CDR2 Asp-52 with Lys 11 and Lys12, and CDR2 Glu-56 with Lys 11. Only one residue in the heavy chain CDR3 is involved, namely Asp-101 with Pro1. The light chain CDR1 is not implicated, whereas several CDR2 residues are involved, Tyr-49 with Lys5, Trp-50 with Pro8 and Tyr-32 from CDR1 interacts with Lys 5. At the carboxyl terminus, interactions involve charged residues. From the light chain CDR1, Asp-27 interacts with Lys24, Asp-28 with Lys 24 and Asp 25, Lys-30 with Asp 25, whereas Tyr-32 from CDR1 interacts with Lys 5. At the carboxyl terminus, interactions involve charged residues. From the light chain CDR1, Asp-27 interacts with Lys 24, Asp-28 with Lys 24 and Asp 25, Lys-30 with Asp 25, whereas Tyr-32 from CDR1 interacts with Lys 5. From the light chain CDR2, only Tyr-91 interacts with Ser3.

For LG2–2 (Fig. 1, C and D), the heavy chain CDR1 residues Tyr-32 and Tyr-35 interact with Pro3 and Glu2, respectively, only involved in distant hydrogen bonds, and this also suggests that the Lys to Ala5 replacement does not dramatically affect the overall structure of the 1–20 H2B peptide recognized by the set of antibodies studied.

Despite the limitations and uncertainties inherent to the modeling process, these studies are in agreement with the results obtained by ELISA, indicating that Pro3 is required for the binding of both LG2–2 and PR1–1 and that Lys11 is important for the optimal binding of all three antibodies. Interestingly, the replacement of Lys5 with an alanine residue had moderate or no effect on antibody reactivity. This is also in good agreement with the model that indicates that this residue is only involved in distant hydrogen bonds, and this also suggests that the Lys to Ala5 replacement does not dramatically affect the overall structure of the 1–20 H2B peptide recognized by the set of antibodies studied. A remarkable and unexpected feature of these modeling studies is that they suggest that the heavy chain CDR3s play only a limited role in direct binding to the histone H2B peptide (although these CDR3s can still play an important role by contributing to the overall V region structure). The heavy chain CDR3 is extremely diverse, since it results from the rearrangement of three different gene segments (VH, D, and JH) and from the extensive joining flexibility that takes place during this rearrangement process. The heavy chain CDR3 is centrally located within the antibody-combining site and is critical for antigen binding. For instance, in anti-chromatin autoantibodies directed against DNA or DNA-histone complexes, the heavy chain CDR3 often contains multiple cationic residues (usually arginine) that are critical for contact with the negatively charged DNA (reviewed in Refs. 2 and 30). For two of our mAbs (LG11–2 and PR1–1), the limited role of heavy chain CDR3 can be in part attributed to the very short lengths of their heavy chain CDR3s (4 residues). In contrast to these two mAbs, a survey of mouse heavy chain CDR3 sequences indicated that

**Table VII**

| mAb    | HCDR1  | HCDR2  | LCDR1 | LCDR2 | LCDR3 |
|--------|--------|--------|--------|--------|--------|
| PR1–1  | SYWMM  | KIDPSDSETHYQKFKD | PLDY  | KASQNVTDYS | WASNRF
| LG2–2  | SYVMM  | VINYPNDCTKYNEFKFG | PDDY  | BSSQSIHVHSNGTYLE | YSHVRT
| LG11–2 | DYMTH  | AIDPETGTAYQNYKLLQ | EVDY  | KSSQSLDSDGKTYLN | LVSKLDS

**Table VIII**

| Antibody | Chain | Protein Data Bank file | Segment grafting | Residue insertion | Residue deletion |
|----------|-------|------------------------|------------------|------------------|-----------------|
| PR1–1    | Light | CRI_1ncavf              | None             | None             | None            |
| PR1–1    | Heavy | CRI_1jhfav              | 94–102 from CRI_1bbjfv.pdb | None             | 96–98           |
| LG2–2    | Light | CRI_1tetfv              | None             | None             | None            |
| LG2–2    | Heavy | CRI_1jhfav              | None             | None             | None            |
| LG11–2   | Light | CRI_4fabfv              | None             | None             | None            |
| LG11–2   | Heavy | CRI_1jhfiv              | 94–102 from CRI_1bbjfv.pdb | None             | 96–98           |

Val-94 with Lys12 and Gly13, and Tyr-96 with Glu2, Lys5, and Ser6.

For LG11–2, which reacts and was modeled with the peptide 1–25 of H2B, the main interactions of the heavy chain CDRs were with lysine residues at the center of the peptide, with Thr-28 and Thr-30 from CDR1 interacting with Lys11, Asp-31 from CDR1 interacting with Lys13, Lys15, and Lys20, whereas Asp-52 from the CDR2 interacts with Lys13 (Fig. 1, E and F). The light chain CDRs interact with determinants located at both peptide termini. Asp-55 and Tyr-49 from CDR2 interact with Pro1, whereas Tyr-32 from CDR1 interacts with Lys5. At the carboxyl terminus, interactions involve charged residues. From the light chain CDR1, Asp-27 interacts with Lys24, Asp-28 with Lys24 and Asp25, Lys-30 with Asp25, whereas Lys-53 from the CDR2 also interacts with Asp25. In our model, neither the heavy nor the light chain CDR3 plays any significant role in peptide binding.
their average length is 8.7 (31). Our results are reminiscent of studies conducted with several anti-lysozyme antibodies that contained heavy chain CDR3s of various lengths (32–35). These observations indicated that the involvement of the heavy chain CDR3 in lysozyme binding is proportional to its length. In contrast, as the heavy chain CDR3 shortens, the heavy chain CDR1 and CDR2 become gradually more involved and interact with a greater number of residues on the lysozyme molecule.

Our analysis therefore supports the view that the length of the heavy chain CDR3 can dramatically influence the importance of the interactions of the other regions of the combining site.

The results obtained in this study are important for our understanding of autoimmune phenomena. They support previous studies indicating that the autoantibodies to histone H2B are mostly directed against a unique segment of the molecule, namely the amino terminus domain. Our data also confirm...
that, despite its limited size, the H2B amino terminus includes several overlapping self-epitopes. There is a general consensus that self-reactive B cells in SLE are directly stimulated by nuclear antigens (2, 30) and there is also increasing evidence that these self-antigens can be presented to the immune system as a result of the apoptotic process (36). Therefore, these results suggest that the histone H2B amino-terminal domain is particularly exposed and immunogenic in chromatin that has been fragmented and adulterated following apoptotic cell death. Our study also helps us to understand the interactions that take place among the various CDR residues in the antibody variable regions and the sequential H2B epitope(s). The immune response to a linear determinant of histone H2B is particularly unique since other autoantibody responses in SLE often involve complex, multimolecular epitopes (37). Future site-directed mutagenesis studies of the anti-H2B autoantibodies CDRs will allow us to elucidate the molecular basis of these interactions.

Acknowledgments—We are grateful to Drs. Marko Radic and Frederic Brard for their insightful comments about the manuscript.

REFERENCES
1. van Holde, K. E. (1989) Chromatin, Springer-Verlag New York Inc., New York
2. Monestier, M. (1997) Methods 11, 36–43
3. Hardin, J. A., and Thomas, J. O. (1983) Proc. Natl. Acad. Sci. U. S. A. 80, 7410–7414
4. Muller, S., Couppez, M., Briand, J. P., Gordon, J., Sautier, P., and Van Regenmortel, M. H. V. (1985) Biochim. Biophys. Acta 827, 235–246
5. Portanova, J. P., Cheronis, J. C., Blodgett, J. K., and Kotzin, B. L. (1990) J. Immunol. 144, 4633–4640
6. Monestier, M., Fasy, T. M., Novick, K. E., and Muller, S. (1993) Mol. Immunol. 30, 1069–1075
7. Hasegawa, M., Sato, S., Kikuchi, K., and Takehara, K. (1998) Ann. Rheum. Dis. 57, 470–475
8. Williams, W. M., Whalley, A. S., Comaschio, R. M., Rosenberg, J., Watts, R. A., Isenberg, D. A., Mccutchan, J. A., and Morrow, W. J. (1996) Clin. Exp. Immunol. 104, 18–24
9. Monestier, M., and Kotzin, B. L. (1992) Rheum. Dis. Clin. N. Am. 18, 415–436
10. Theofilopoulos, A. N., and Dixon, F. J. (1985) Adv. Immunol. 37, 269–390
11. Monestier, M., and Novick, K. E. (1996) Mol. Immunol. 33, 89–99
12. Benkirane, N., Guichard, G., Van Regemortel, M. H. V., Briand, J.-P., and Muller, S. (1995) J. Biol. Chem. 270, 11921–11926
13. Salgany, P., Varadachary, A. S., Primiano, L. L., Fincke, J. E., Muller, S., and Monestier, M. (1997) Nucleic Acids Res. 25, 680–681
14. Stemmer, C., Briand, J. P., and Muller, S. (1997) J. Mol. Biol. 273, 52–60
15. Stemmer, C., Richalet-Scordel, P., van Bruggen, M., Kramers, K., Berden, J., and Muller, S. (1996) J. Biol. Chem. 271, 21257–21261
16. Neimark, J., and Briand, J. P. (1993) Pept. Res. 6, 219–228
17. Quesnel, A., and Briand, J. P. (1989) J. Pept. Res. 32, 107–111
18. Barakat, S., Briand, J. P., Weber, J. C., Van Regenmortel, M. H. V., and Muller, S. (1990) Clin. Exp. Immunol. 81, 256–262
19. Badley, J. E., Bishop, G. A., St. John, T., and Frelinger, J. A. (1988) Biotechniques 6, 114–116
20. Geliebert, J. (1987) Focus 9, 5–10
21. Monestier, M. (1991) Eur. J. Immunol. 21, 1725–1731
22. Monestier, M., Stemmer, C., Ong, G. L., and Muller, S. (1997) Mol. Immunol. 34, 39–51
23. Devereux, J., Haeberli, P., and Smithies, O. (1984) Nucleic Acids Res. 12, 387–395
24. Mandal, C., Kingery, B. D., Anchin, J. M., Sribaraman, S., and Linthicum, D. S. (1996) Nat. Biotechnol. 14, 323–328
25. Kingery, B. D., Culperton, C., and Linthicum, D. S. (1996) Biotechnol. Software J. 13, 20–27
26. Gabriel, J. L., and Mitchell, W. M. (1993) Proc. Natl. Acad. Sci. U. S. A. 90, 4186–4190
27. Briand, J. P., Guichard, G., Damor, H., and Muller, S. (1995) J. Biol. Chem. 270, 20866–20091
28. Briand, J. P., Benkirane, N., Guichard, G., Newman, J. F., Van Regenmortel, M. H. V., Brown, F., and Muller, S. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 12545–12550
29. Kabat, E. A., Wu, T. T., Perry, H. M., Gottesman, K. S., and Foeller, C. (1991) Sequences of Proteins of Immunological Interest, U. S. Government Printing Office, Bethesda, MD
30. Racie, M. Z., and Weigert, M. (1994) Annu. Rev. Immunol. 12, 487–520
31. Wu, T. T., Johnson, G., and Kabat, E. A. (1993) Proteins 16, 1–7
32. Amit, A. G., Mariuzza, R. A., Phillips, S. E., and Poljak, R. J. (1986) Science 233, 747–753
33. Padlan, E. A., Silverton, E. W., Sheriff, S., Cohen, G. H., Smith-Gill, S. J., and Davies, D. R. (1989) Proc. Natl. Acad. Sci. U. S. A. 86, 5938–5942
34. Sheriff, S., Silverton, E. W., Padlan, E. A., Cohen, G. H., Smith-Gill, S. J., Finzel, B. C., and Davies, D. R. (1987) Proc. Natl. Acad. Sci. U. S. A. 84, 8075–8079
35. Kabat, E. A., and Wu, T. T. (1991) J. Immunol. 147, 1709–1719
36. Casciola-Rosen, L. A., Anhalt, G., and Rosen, A. (1994) J. Exp. Med. 179, 1317–1330
37. Bursling, R. W., and Rubin, R. L. (1996) Mol. Biol. Rep. 23, 159–166
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J. Biol. Chem. 2000, 275:13558-13563.
doi: 10.1074/jbc.275.18.13558

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