

## Shared idiotypes are expressed on mouse and human anti-DNA autoantibodies

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**Summary.** The expression of common idiotypes on human and mouse anti-DNA monoclonal autoantibodies made by hybridomas was examined by their competitive binding to anti-idiotype antibodies. Some murine autoantibodies inhibited the binding of a human anti-DNA autoantibody 16/6 to monoclonal or polyclonal anti-idiotypic antibodies. Another human antibody (134) was not inhibited in its binding to homologous anti-idiotypic antibodies.

The expression of the human 16/6 idio type on mouse antibodies was restricted to those that had a specificity similar to the 16/6 antibody itself, their major properties being that they reacted more strongly with single stranded DNA (ssDNA) than double stranded DNA (dsDNA). One mouse antibody expressing the 16/6 idio type also bound weakly to RNA. The results imply structural similarities between the binding sites of the antibodies in the two species, and are consistent with evolutionary conservation of V genes coding for primitive ancestral antibodies that react with DNA and become diversified through somatic mutation.

Abbreviations: CII, collagen type II; DNA, deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; HPGM, human proteoglycan monomer; MRL/*lpr*, MRL/*Mp-lpr/lpr*; PBS, phosphate-buffered saline; RNA, ribonucleic acid; SLE, systemic lupus erythematosus.

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## INTRODUCTION

The syndromes of human systemic lupus erythematosus (SLE) and murine lupus are characterized by the spontaneous development of autoantibodies which react with polynucleotides, phospholipids and many other intracellular components (Tan, 1982). In order to analyse more closely the precise ligand binding specificity of antibodies normally found only as mixtures in the serum, a number of groups have prepared sets of monoclonal antibodies from mice with lupus-like disease (Andrzejewski *et al.*, 1980; Hahn *et al.*, 1980; Morgan, Buchanan & Staines, 1982; Marion *et al.*, 1982; Koike *et al.*, 1982; Morgan *et al.*, 1985) and from human patients with SLE (Shoenfeld *et al.*, 1983b; Rauch, Massicotte & Tannenbaum, 1985). Three main populations of DNA-binding autoantibodies have been described: those that are specific for double stranded DNA (dsDNA) and single stranded DNA (ssDNA) respectively, and those that react with both forms of DNA. We have reported previously that antibodies in the last population can be further subdivided into three groups on the basis of the extent of their relative reactions with the two physical forms of the DNA (Morgan *et al.*, 1982, 1985).

Many monoclonal anti-DNA autoantibodies are clearly bispecific or multispecific, in that they also react with a number of seemingly unrelated antigens such as phospholipids (Shoenfeld *et al.*, 1983b; Rauch

*et al.*, 1984, 1985; Staines, Thompson & Morgan, 1985), vimentin (Haskard *et al.*, 1985; Andre-Schwartz *et al.*, 1984), rheumatoid factor (Rubin *et al.*, 1984), proteoglycan (Faaber *et al.*, 1984), cell surface proteins (Jacob *et al.*, 1984) and *Klebsiella* antigens (Naparstek *et al.*, 1985). These cross-reactions are likely to be due, in some cases, to the sharing of common epitopes such as the phosphodiester links separated by three carbon atoms on both DNA and cardiolipin (Lafer *et al.*, 1981).

Idiotypic analyses of monoclonal anti-DNA autoantibodies derived from either humans or mice have shown that many share common or cross-reacting idiotypes (Tron *et al.*, 1982; Marion *et al.*, 1982; Shoenfeld *et al.*, 1983a; Solomon *et al.*, 1983), although not all antibodies of even very similar specificity necessarily share idiotypes (Tron, Jacob & Bach, 1983; A. Morgan and N. A. Staines, manuscript in preparation).

In order to extend further our knowledge of idiotypic sharing by DNA reactive antibodies, we have conducted an idiotypic analysis of two monoclonal human hybridoma anti-DNA autoantibodies (16/6 and 134) (Shoenfeld *et al.*, 1983b) and a library of monoclonal hybridoma anti-DNA autoantibodies derived from mice with lupus-like disease (Morgan *et al.*, 1985), and report here that anti-DNA antibodies of similar specificity from humans and mice can share the same idiotypes.

## MATERIALS AND METHODS

### *Human and mouse monoclonal anti-DNA antibodies*

The preparation, affinity purification and properties of

the human hybridoma anti-DNA autoantibodies (16/6 and 134, both IgM-k) have been described by Shoenfeld *et al.* (1983b). Both antibodies bind ssDNA but also react with other polynucleotides, including poly dT, poly I and dsDNA. Antibody 16/6 reacts preferentially with ssDNA and antibody 134 with dsDNA.

The derivation and properties of the library of mouse monoclonal anti-DNA autoantibodies from MRL/Mp-*lpr/lpr* (MRL/*lpr*) and (NZB × NZW)<sub>F</sub><sub>1</sub> mice with lupus-like disease have been described by Morgan *et al.* (1985). The autoantibodies have been classified into Groups I–V on the basis of their ligand-binding reactions which are summarized in Table 1. Antibodies representative of all specificity groups, heavy chain isotypes M, G1, G2a and G2b and both mouse strains were used in these experiments.

All mouse monoclonal antibodies used here were purified from ascites fluids or culture supernatant (mouse antibody 88 only) by affinity chromatography on protein-A sepharose (Sigma Chemical Company, Poole, Dorset). This was used according to the supplier's general instructions: antibody-containing fluids were diluted in 100 mM phosphate buffer, pH 8.0, for adsorption, and antibody was eluted with 115 mM citrate-phosphate buffer, pH 2.8.

Mouse Ig concentrations were determined by radial immunodiffusion using commercially prepared plates (Serotec, Blackthorn, Oxon) and by inhibition enzyme-linked immunosorbent assay (ELISA) (A. Morgan & N. A. Staines, manuscript in preparation). In the latter, the unknown samples were quantified against a standard by titrating their ability to inhibit the binding of (a limiting amount of) an enzyme-

**Table 1.** Taxonomy of DNA-reactive monoclonal murine antibodies

Group	Antibodies	Antigenic determinant recognized
I	33	Conformational determinants expressed on dsDNA only
II	28,112,402, 405,410	Conformational determinants expressed on both ssDNA and dsDNA
III	152	Determinants on ssDNA expressed weakly on dsDNA
IV	127,207,223, 228,406	Base-dependent determinants on ssDNA
V	32,88,	Determinants on ssDNA expressed weakly on dsDNA and RNA

Further information on the properties of the antibodies is given by Morgan *et al.* (1985).

labelled rabbit anti-mouse Ig reagent to immobilized mouse Ig.

#### Anti-idiotypic antibodies and antisera

Details of the preparation and properties of the anti-idiotypic reagents have been published. The rabbit anti-human idiotypic antisera, anti-16/6-R and anti-134-R, have been described by Shoenfeld *et al.* (1983a). The mouse monoclonal anti-idiotypic antibody (anti-16/6 M) specific in its reaction with antibody 16/6 was also prepared as described by Andrzejewski *et al.* (1980). The anti-idiotypic reagents have all been shown to inhibit the binding of idiotypic to antigen (Shoenfeld *et al.*, 1983a). Anti-16/6-M was inhibited in its binding to human autoantibody 16/6 by antibody 16/6 itself and human monoclonal anti-

bodies 21/28, 32/9, 18/2 and 15/14 which have a specificity similar to 16/6 but not by other human monoclonal antibodies tested (see Fig. 3 in Shoenfeld *et al.*, 1983b).

#### Competitive inhibition ELISA for estimation of idiotypic sharing between human and mouse antibodies

Flat-bottomed 96-well (Immulon II) ELISA plates (Dynatech, Billingshurst, Sussex) were coated overnight at 4° with human anti-DNA antibodies 16/6 or 134 (0.25 µg/ml) in 0.05 M borate buffer, pH 8.6. Wells were washed three times with 1% Tween 20 (Sigma Chemical Co.) in phosphate-buffered saline (PBS) and then PBS alone. Limiting amounts of anti-idiotypic antibodies (working dilutions of all reagents were greater than 1/10,000) were incubated with sequential

**Table 2.** Idiotypic sharing between human and mouse anti-DNA autoantibodies

Competing monoclonal antibody						
				Concentration giving 50% inhibition (µg/ml)		
				Human monoclonal		
				16/6	134	
				Anti-idiotypic antibody		
Group	No.	Strain	H chain type	anti-16/6-R	anti-16/6-M	anti-134-R
I	33	BWF <sub>1</sub>	2a	—*	—	—
II	402	MRL/lpr	2a	26	3.8	—
	410	MRL/lpr	2a	—	0.41	—
	28	BWF <sub>1</sub>	2a	7.5	1.0	—
	112	BWF <sub>1</sub>	2b	16	—	—
	405	MRL/lpr	2a	—	—	—
III	152	MRL/lpr	2a	—	—	—
IV	127	MRL/lpr	2a	—	—	—
	207	MRL/lpr	2a	—	—	—
	223	MRL/lpr	1	—	—	—
	228	MRL/lpr	2a	—	—	—
V	406	MRL/lpr	2a	—	—	—
	32	BWF <sub>1</sub>	1	—	—	—
	88	BWF <sub>1</sub>	1	—	0.05	—
	16/6	Human SLE	M	0.027	0.12	—
	134	Human SLE	M	—	—	0.18
HPGM†	419	MRL/lpr	M	—	—	—
CII‡	16	DBA/1	1	—	—	—

\* —, No inhibition seen at 1500 µg/ml.

† HPGM, human proteoglycan monomer.

‡ CII, Type II Collagen.

dilutions of mouse monoclonal anti-DNA antibodies for 1 hr at room temperature, then applied to the idiotype-coated wells for 2 hr. After washing, 150  $\mu$ l of an appropriate goat anti-rabbit or a rabbit anti-mouse immunoglobulin reagent conjugated to alkaline phosphatase (Miles Laboratories, Slough, Berks) were added and the plates were incubated overnight at 4°. The assay was concluded as described by Shoenfeld *et al.* (1983a).

## RESULTS

### Expression of human idiotypes on mouse immunoglobulins

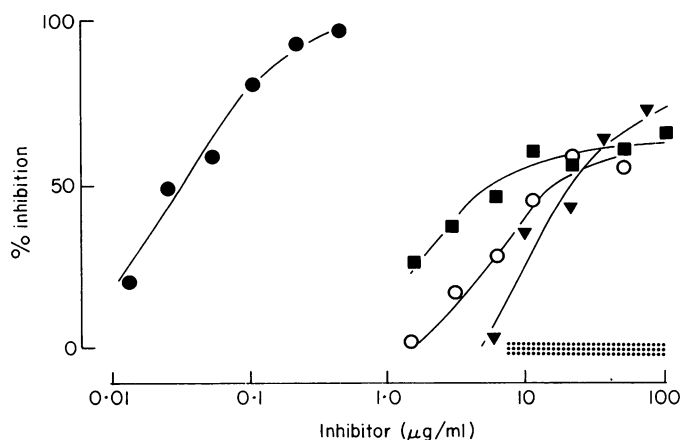
Five out of the 14 mouse monoclonal antibodies tested reacted with the anti-16/6 idiotype reagents. None of the mouse antibodies appeared to react with the anti-134 idiotype reagent (Table 2). The reaction of the 16/6 idiotype-bearing antibody with both anti-16/6R and anti-16/6M appeared to be specific, in that other mouse monoclonal antibodies such as those directed against Type II Collagen (antibody 1083-16) or human proteoglycan monomer (antibody 1094-419) (gifts of S. Omar and R. A. Lake, respectively) and normal mouse serum immunoglobulin were not inhibitory. There was no association of inhibitory activity, or the lack of it, with heavy chain isotype or strain of origin of the antibodies.

### Reaction of murine anti-DNA antibodies with rabbit polyclonal anti-human anti-idiotypic antisera

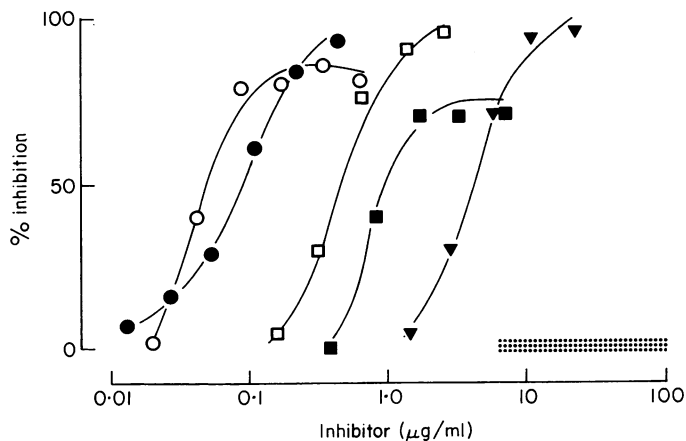
Murine autoantibodies 402, 112 and 28 inhibited the binding of rabbit anti-16/6-R to 16/6 by 50% at concentrations of 26, 16 and 7.5  $\mu$ g/ml, respectively. These concentrations of inhibitions were at least 1000 $\times$  greater than the amount of the homologous human antibody (16/6) required for comparable inhibition (Fig. 1). The 11 other anti-DNA autoantibodies did not affect the interactions of the rabbit anti-idiotypic reagent and the human antibody, even at concentrations of 1500  $\mu$ g/ml. The inhibitory mouse antibodies are all members of specificity Group II (Table 1).

### Reaction of murine anti-DNA monoclonal antibodies with murine monoclonal anti-human anti-idiotypic antibody

The binding of the mouse monoclonal antibody anti-16/6-M to the human 16/6 antibody was inhibited by the mouse antibodies 402, 28, 410 and 88 at concentrations of 3.8, 1.0, 0.41 and 0.05  $\mu$ g/ml, respectively (for 50% inhibition). However, in contrast to the results obtained with the polyspecific anti-16/6-R antiserum, the amounts required for this inhibition were much closer to the amount (0.12  $\mu$ g/ml) of homologous human 16/6 antibody required for the same degree of inhibition (Fig. 2).



**Figure 1.** Competition between mouse and human DNA-reactive monoclonal antibodies for binding to rabbit anti-16/6-R anti-idiotypic antibodies. Competing monoclonal antibodies: (●) 16/6; (■) 28; (▼) 402; (○) 112; (□) non-inhibitory antibodies. See Table 1 for details of all antibodies.



**Figure 2.** Competition between mouse and human DNA-reactive monoclonal antibodies for binding to mouse monoclonal anti-16/6-M anti-idiotype antibody. Competing monoclonal antibodies: (●) 16/6; (■) 28; (▼) 402; (○) 88; (□) 410; (▣) non-inhibitory antibodies. See Table 1 for details of all antibodies.

Antibodies 28, 402 and 410 are members of specificity Group II and have similar ligand binding characteristics to human autoantibody 16/6. Antibody 88 is, however, a member of Group V and was the most potent inhibitor in these experiments, having the same order of activity as the homologous human antibody. The specificity of this antibody was closer to autoantibody 16/6 than the group II autoantibodies, reacting strongly and preferentially with ssDNA and also reacting with other polynucleotides. The 10 other mouse anti-DNA antibodies examined were not inhibitory at concentrations up to 1500 µg/ml.

## DISCUSSION

The lupus-like diseases of (NZB × NZW)<sub>F</sub><sub>1</sub> and MRL/*lpr* mice resemble human SLE in their clinical and pathological features (Andrews *et al.*, 1978; Theofilopoulos & Dixon, 1982). We have demonstrated here that the similarities extend further to include idiotypic sharing in antibodies that characteristically react with both ssDNA and dsDNA. Shared idiotypic correlated with ligand binding specificity, suggesting that the common idiotypes included the antigen-binding site.

We show elsewhere that, within the library of mouse monoclonals derived from MRL/*lpr* and (NZB × NZW)<sub>F</sub><sub>1</sub> mice, idiotypes are shared between DNA-reactive antibodies of different specificity and that antibodies of similar specificity may have differ-

ent idiotypes (A. Morgan and N. A. Staines, manuscript in preparation). Hahn & Ebling (1984) have shown that a public idiotypic determinant is present on cationic IgG anti-DNA antibodies from (NZB × NZW)<sub>F</sub><sub>1</sub>, MRL/*lpr* and BXSB mice. They noted that antibodies carrying the same idiotypic bound to different epitopes on the DNA molecule. This report extends these findings to show that antibodies within a specificity group share idiotypes not found on antibodies of other specificities, and that this sharing extends to two different species.

The 16/6 idiotypic was found on mouse anti-DNA autoantibodies that had an antigen-binding profile similar to that of the human autoantibody. On the basis of the results from the competitive inhibition assay, the mouse antibody 88 showed the greatest expression of the idiotypic, and this antibody was the closest of the antibodies examined to the human antibody in its ligand-binding profile, being reactive with ssDNA, dsDNA, RNA (similar to poly I with which 16/6 reacts) but not with cardiolipin (Staines *et al.*, 1985).

There were quantitative differences in the extent of inhibition seen with the murine antibodies. These are interpreted to indicate that the 16/6 idiotypic, as defined by the rabbit anti-idiotype antiserum, is polymorphic, and that different combinations of idiotypic components of it are expressed in the individual mouse antibodies.

The mouse antibodies that express the 16/6 idiotypic have similar epitope-binding specificity. It has been

shown elsewhere that 30 other human DNA-reactive monoclonal antibodies also express the 16/6 idiotype. The present results might indicate that the anti-16/6-M monoclonal antibody and the polyclonal anti-16/6-R serum antibodies express or include an internal image of the autoantigen. In the absence of data on the ability of the anti-idiotypic reagents to inhibit the binding of the 16/6 idiotype-bearing antibodies to DNA, no definite conclusion can be made about this possibility. The identity of the epitope on the DNA with which the antibodies react is not known, but it is probably a conformational determinant expressed on ssDNA more than on dsDNA because of the ligand-binding characteristics of the antibodies (Morgan *et al.*, 1985). We know from other studies that SLE sera contain antibodies that compete with the mouse monoclonal antibodies for the same sites on DNA, reinforcing further the similarities between human and murine DNA-binding antibodies (N. A. Staines, H. S. G. Thompson, A. Morgan, P. Mumford and R. N. Maini, manuscript in preparation). The present results also indicate that there may be structural similarities between human and mouse anti-DNA antibodies at or near to the antigen-combining site. Whether this structural similarity extends to the primary gene sequence has yet to be established. Our observations are supported by a recent study (Eilat, Fischel & Zlotnik, 1985) which identified a shared idiotype, designated A52, on purified IgG fractions from human lupus serum and serum from (NZB × NZW)<sub>F1</sub> mice.

As discussed elsewhere (Lake *et al.*, 1985), the relationship of antibody specificity to pathogenicity is a matter of debate, but antibodies reactive with dsDNA may be especially important in the development of glomerulonephritis. Idiotypic sharing between such supposedly important antibodies in man and mouse supports the common aetiopathogenesis of the diseases in the two species. The human and mouse antibodies that share the 16/6 idiotypes tend to be those that are multispecific; the murine anti-DNA monoclonal autoantibodies that are unispecific for dsDNA or ssDNA did not, in these experiments, share idiotypes with human anti-DNA autoantibodies 16/6 or 134. The possibility exists that the multispecific antibodies are closely related to 'ancestral antibodies' which may be primarily reactive with antigens other than DNA and which may be highly conserved for protection against infection. Analysis of the N-terminal amino acid sequences of the human monoclonal autoantibody 16/6 has shown 95% light chain and 85% heavy chain homology with a macroglobulinaemia

monoclonal IgM (WEA) that binds to *Klebsiella* polysaccharide K.30. (Naparstek *et al.*, 1985).

DNA-reactive autoantibodies may be derived from an ancestral antibody by a process of somatic mutation or variation as illustrated by Griffiths *et al.* (1984) in their studies on V gene stability. Diamond & Scharff (1984) have reported that a single amino-acid substitution in the heavy chain V region of a monoclonal T15+ anti-phosphocholine monoclonal antibody resulted in the loss of its phosphocholine-binding activity. The mutated antibody, however, acquired the ability to bind to phosphorylated macromolecules, including dsDNA. The expression of shared idiotypes on antibodies with similar multispecific binding profiles suggests a common aetiology for lupus diseases in the aberrant or uncontrolled expression of an ancestral antibody and its somatic variants.

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#### REFERENCES

- ANDRE-SCHWARTZ J., DATTA S.K., SHOENFELD Y., ISENBURG D.A., STOLLAR B.D. & SCHWARTZ R.S. (1984) Binding of cytoskeletal proteins by monoclonal anti-DNA lupus autoantibodies. *Clin. Immunol. Immunopathol.* **31**, 261.
- ANDREWS B., EISENBERG R.A., THEOFILOPOULOS A.N., IZUI S.I., WILSON C.B., MCCONAHEY P.J., MURPHY E.D., ROTHS J.B. & DIXON F.J. (1978) Spontaneous murine lupus-like syndromes. Clinical and immunopathological manifestations in several strains. *J. exp. Med.* **148**, 1198.
- ANDRZEJEWSKI C., STOLLAR D.B., LALOR T.M. & SCHWARTZ R.S. (1980) Hybridoma autoantibodies to DNA. *J. Immunol.* **124**, 1499.
- DIAMOND B. & SCHARFF M.D. (1984) Somatic mutation of the T15 heavy chain give rise to an antibody with autoantibody specificity. *Proc. natn. Acad. Sci. U.S.A.* **81**, 5841.
- EILAT D., FISCHEL R. & ZLOTNIK A. (1985) A central anti-DNA idiotype in human and murine systemic lupus erythematosus. *Eur. J. Immunol.* **15**, 368.
- FAABER P., CAPEL P.J.A., RJIKE G.P.M., VIERWINDEN G., VAN DER PUTTE L.B.A. & KOENE R.A.P. (1984) Cross-reactivity of anti-DNA antibodies with proteoglycans. *Clin. exp. Immunol.* **55**, 502.
- GRIFFITHS G.M., BEREK C., KAARTINEN M. & MILSTEIN C. (1984) Somatic mutation and the maturation of immune response to 2-phenyl oxazolone. *Nature (Lond.)*, **312**, 271.

- HAHN B.H. & EBLING F. (1984) A public idiotypic determinant is present on spontaneous cationic antibodies to DNA from mice of unrelated lupus-prone strains. *J. Immunol.* **133**, 3015.
- HAHN B.H., EBLING F., FREEMAN S., CLEVINGER B. & DAVIE J. (1980) Production of monoclonal murine antibodies to DNA by somatic cell hybrids. *Arth. Rheum.* **23**, 945.
- HASKARD D.O., GUL V., MORGAN A., KATAHAHA P., STAINES N.A. & ARCHER J.R. (1985) Cross-reactive human monoclonal autoantibodies from patients with rheumatoid arthritis against intracellular constituents. *Clin. exp. Immunol.* (in press).
- JACOB L., TRON F., BACH J.-F. & LOUARD D. (1984) A monoclonal anti-DNA antibody also binds to cell surface protein(s). *Proc. natn. Acad. Sci. U.S.A.* **81**, 3842.
- KOIKE T., NAGASAWA R., NAGATA N. & SHIRAI T. (1982) Specificity of mouse hybridoma antibodies to DNA. *Immunol. Lett.* **4**, 93.
- LAFER E.M., RAUCH J., ANDRZEJEWSKI C., MUDD D., FURIE B., FURIE B., SCHWARTZ R.S. & STOLLARD B.D. (1981) Polyspecific monoclonal lupus autoantibodies reactive with both polynucleotides and phospholipids. *J. exp. Med.* **153**, 897.
- LAKE R.A., MORGAN A., HENDERSON B. & STAINES N.A. (1985) A key role for fibronectin in the sequential binding of native dsDNA and monoclonal anti-DNA antibodies to components of the extracellular matrix: its possible significance in glomerulonephritis. *Immunology*, **54**, 389.
- MARION T.N., LAWTON A.R., KEARNEY J.F., & BRILES D.E. (1982) Anti-DNA autoantibodies in (NZB × NZW)<sub>F</sub><sub>1</sub> mice are clonally heterogeneous, but a majority share a common idio type. *J. Immunol.* **128**, 668.
- MORGAN A., BUCHANAN R.R.C., LEW A.M., OLSEN I. & STAINES N.A. (1985) Five groups of antigenic determinants on DNA identified by monoclonal antibodies from (NZB × NZW)<sub>F</sub><sub>1</sub> and MRL/Mp-*lpr/lpr* mice. *Immunology*, **55**, 75.
- MORGAN A., BUCHANAN R.R.C. & STAINES N.A. (1982) Monoclonal anti-DNA antibodies, serology and immunofluorescence. *Clin. Rheumatol.* **1**, 65.
- NAPARSTEK Y., DUGGAN D., SCHATTNER A., MADAIO M.P., GONI F., FRANGIONE B., STOLLAR B.D., KABAT E.A. & SCHWARTZ R.S. (1985) Immunochemical similarities between monoclonal antibacterial Waldenström's macroglobulins and monoclonal anti-DNA lupus autoantibodies. *J. exp. Med.* **161**, 1525.
- RAUCH J., MASSICOTTE H. & TANNENBAUM H. (1985) Hybridoma anti-DNA autoantibodies from patients with rheumatoid arthritis and systemic lupus erythematosus demonstrate similar nucleic acid binding characteristics. *J. Immunol.* **136**, 180.
- RAUCH J., TANNENBAUM H., STOLLAR B.D. & SCHWARTZ R.S. (1984) Monoclonal anti-cardiolipin antibodies bind to DNA. *Eur. J. Immunol.* **14**, 529.
- RUBIN R.L., BALDERAS R.S., TAN E.M., DIXON F.J. & THEOFILOPOULOS A.N. (1984) Multiple autoantigen binding capabilities of mouse monoclonal antibodies selected for rheumatoid factor activity. *J. exp. Med.* **159**, 1429.
- SHOENFELD Y., ISENBERG D.A., RAUCH J., MADAIO M.P., STOLLAR B.D. & SCHWARTZ R.S. (1983a) Idiotypic cross-reactions of monoclonal human lupus autoantibodies. *J. exp. Med.* **158**, 718.
- SHOENFELD Y., RAUCH J., MASSICOTTE H., DATTA S.K., ANDRE-SCHWARTZ J., STOLLAR B.D. & SCHWARTZ R.S. (1983b) Polyspecificity of monoclonal lupus autoantibodies produced by human-human hybridomas. *New Engl. J. Med.* **308**, 414.
- SOLOMON G., SCHIFFENBAUER J., KEISER H.D. & DIAMOND B. (1983) Use of monoclonal antibodies to identify shared idiotypes on human antibodies to native DNA from patients with systemic lupus erythematosus. *Proc. natn. Acad. Sci. U.S.A.* **80**, 850.
- STAINES N.A., THOMPSON H.S.G. & MORGAN A. (1985) Diversity and multispecificity of autoantibodies reactive with DNA: some evolutionary implications. *Protides Biol. Fluids*, **33**, (in press).
- TAN E.M. (1982) Autoantibodies to nuclear antigens (ANA) their immunobiology and medicine. *Adv. Immunol.* **33**, 167.
- THEOFILOPOULOS A.N. & DIXON F.J. (1982) Autoimmune diseases: immunopathology and etiopathogenesis. *Am. J. Pathol.* **108**, 321.
- TRON F., JACOB L. & BACH J.-F. (1983) Murine monoclonal anti-DNA antibodies with an absolute specificity for DNA have a large amount of idiotypic diversity. *Proc. natn. Acad. Sci. U.S.A.* **80**, 6024.
- TRON F., LE GUERN C.L., CAZENAVE P.-A. & BACH J.-F. (1982) Intrastrain recurrent idiotypes among anti-DNA antibodies of (NZB/NZW)<sub>F</sub><sub>1</sub> hybrid mice. *Eur. J. Immunol.* **12**, 761.