The molecular recognition theory applied to bispecific antibodies . . .

To the editor — In a previous issue of *Nature Medicine*, J. Edwin Blalock outlined the potential importance of the molecular recognition theory (MRT) to our understanding of the structure–function relationship of proteins and peptides[1]. In the same issue, Baranyi *et al.*[2] describe a new structural motif in proteins, the antisense homology box (AHB), which may represent intra- and intermolecular recognition sites in proteins and peptides. The MRT could readily explain, at the molecular level, our recent finding of the so-called TGPO autoantibodies, bispecific autoantibodies reacting with thyroglobulin (Tg) and thyroperoxidase (TPO), two major antigens involved in thyroid autoimmune disease.

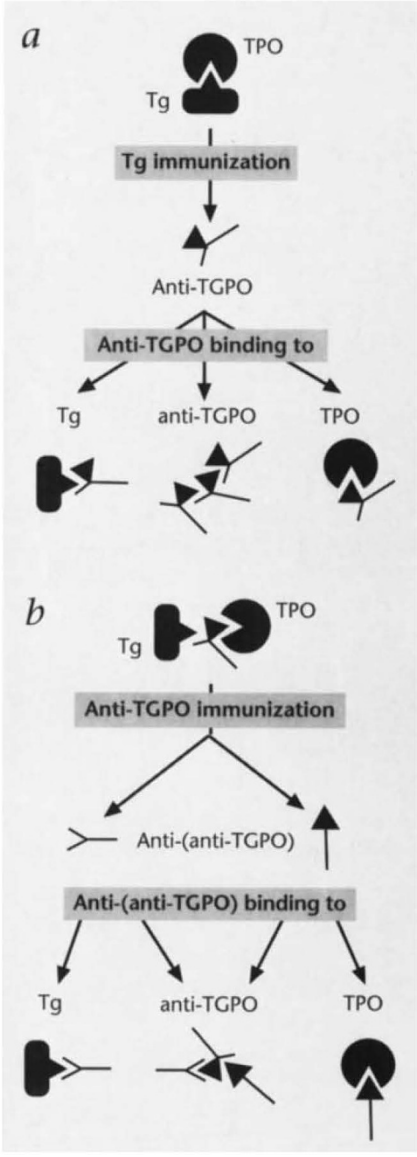

Figure *a*, Tg and TPO interact together as a substrate–enzyme pair to form the thyroid hormones. Immunization with Tg induces TGPO antibodies that bind to Tg and TPO and behave as self-binding antibodies. *b*, Immunization with TGPO antibodies yields antibodies complementary to TGPO antibodies, Tg and TPO.

The possibility of epitopic similarity between Tg and TPO as an explanation for TGPO autoantibody cross-reactivity was ruled out by amino acid sequence and peptide analysis. However, it came to light that TGPO autoantibodies displayed two different binding sites on the immunoglobulin variable regions. One is specific for Tg — probably the paratope — and a second one — an idiotope — reacts with TPO (ref. 3). Complementarity between the paratope and the idiotope was demonstrated by a significant self-binding of TGPO autoantibodies and production of both Tg and TPO antibodies after immunization of mice with TGPO $F(ab')_2$ autoantibodies. A schematic representation of these interactions between Tg, TPO and their antibody counterparts is shown in the figure. Each interaction demands complementary structures that could involve interacting complementary peptides derived, according to the MRT, from complementary or antisense nucleotide sequences.

While complementary peptides have been independently associated with a variety of interacting peptides, so far they have not been implicated in interacting autoantigens and their corresponding antibodies. Our observation that TGPO antibodies may simultaneously bind Tg and TPO on separate interactive structures fits rather well with the proposed AHB theory. The paratope of the TGPO autoantibodies would bind to the major hormonogenic site of human Tg, and this site, which should obviously interact with TPO to form thyroid hormones, would be complementary to both TPO and the paratope of the TGPO autoantibodies. Alternatively, an antisense idiotope complementary to the paratope would account for the binding of TPO to TGPO autoantibodies.

It would seem worthwhile to examine antibodies directed against complementary structures of interacting antigens, such as hormones and cognate receptors, for the presence of antisense sequences. This may improve our understanding of the autoimmune mechanisms leading to diseases implicating interacting autoantigens.

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. . . but not to protein folding?

To the editor — Blalock[1] discusses the study of Baranyi *et al.*[2] concerning antisense homology boxes (AHB) within protein molecules in which AHBs consist of amphiphilic peptides and corresponding antisense peptides separated by approximately 50 amino acids. In both articles there is speculation that AHBs may represent intra- and intermolecular recognition sites in proteins.

To investigate this possibility, we have analysed several proteins of known crystal structure. Thirty-four proteins were taken from the representative (non-homologous) set of structures in the Protein Data Bank[4]: 1AVH, 1BAB, 1DNK, 1END, 1FAS, 1FCS, 1FDD, 1FXI, 1GKY, 1MUP, 1OMP, 1OSA, 1PAF, 1PAZ, 1PHB, 1RND, 1SBP, 2AAA, 2CPL, 2HAD, 2LIV, 2PIA, 2RN2, 2SN3, 3ADK, 3CD4, 3DFR, 4FXN, 4GCR, 4SBV, 8CAN, 9RNT, 1L92, 1TIE. Within this set there are, using the original criteria of Baranyi *et al.* (ten-amino acid-wide frame and eight or more amino acids required to be antisense), only ten antisense homology boxes in nine proteins (1AVH, 1FXI, 1GKY, 1PHB, 2AAA, 2PIA, 4GCR, 8ACN and 1L92), and in none of these do the sense and antisense fragments interact