RESEARCH PAPER ANALYSIS

MIGIS PEPTIDES TO TARGET B CELL SUBTYPES

The different classes of antibody-producing B cells are distinguished by the type of immunoglobulin (Ig) they secrete and also display on their surfaces as antigen receptors. Imbalances in these classes are responsible for disorders as diverse as immunodeficiencies, allergies, autoimmunities, and malignancies. In this issue of *Bio/Technology*, Tse Wen Chang and his colleagues at Tanox Biosystems (Houston, TX) provide a solution to the elusive problem of specifically targeting these B cell subtypes.

Their success depends on the ability to raise monoclonal antibodies (MAbs) that are isotype specific (to distinguish the Ig subclasses) but which *only* bind to membrane-anchored immunoglobulins. Structurally these Igs differ from their secreted forms by carboxyl-terminus extensions of the heavy chains that fix them to the B cell surface. As Chang discovered, the sequences of the membrane-anchoring segments are themselves isotype specific. The scientists therefore sought MAbs that would recognize the extracellular domains of these segments, which they have termed *migis* (membrane-bound

Ig isotype-specific) peptides.

Using a synthetic peptide corresponding to a predicted *migis* epitope of human IgE as a primary immunogen, the researchers were able to clone a hybridoma that secreted a mouse immunoglobulin with all the expected properties of an anti-*migis* MAb. The antibody bound tightly to a *migis*- ϵ peptide, and to human cell lines that express IgE on their surfaces. It did not react at all with *migis* peptides of the other Ig isotypes, with any type of purified soluble Ig, or with a variety of non-IgE-secreting immune system cells.

Thus *migis* peptides not only specifically mark B cell subsets, they are also accessible to antibodies prepared against them. As such, these peptides and their corresponding MAbs represent exciting new tools with potential applications in diagnosis, therapy, and basic research. For example, anti-*migis* MAbs could be used to monitor B cell subtype profiles in a variety of clinical settings.

While such uses are relatively straightforward, therapeutic utility depends on demonstrating that these antibodies can modulate the activity

of B cell subsets *in vivo* via receptor interactions or by their ability to promote cytotoxicity. A first test of this could be the use of a humanized version of the anti-membrane IgE antibody to suppress IgE production in allergy patients.

Like the anti-IgE MAbs Chang described earlier (*Bio/Technology* 8:122, Feb '90), the present antibodies will not react with IgE bound to mast cells or basophils via Fc receptors, and therefore will not induce histamine release. Unlike these antibodies, however, they are equally unreactive with soluble IgE. Thus, while they cannot be expected to eliminate circulating antibodies, neither do they have the potential to form immune complexes.

In attempting to target other types of Ig-producing cells, non-reactivity with the soluble form also means that the injected MAb will not be cleared before reaching the target B cell subtype. This becomes particularly important in the possible use of anti-*migis* MAbs to treat diseases like rheumatoid arthritis or B cell leukemias, where the concentrations of the relevant Igs in the circulation will be quite high.

—Harvey Bialy

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BIOTRANSFORMATION TECHNOLOGIES SCALED UP

LONDON—"Growing awareness of toxic effects of chemicals in the biosphere, combined with recognition of the enormous benefits of pesticides, therapeutic agents, and other substances, is generating a strong demand for more selective drugs and for pesticides targeted in their mode of action," said Jan Kamphuis of DSM Research (Geleen, The Netherlands), speaking at a symposium held here by the Biotechnology Group of the Royal Society of Chemistry. "Not least because nature itself is intrinsically chiral at the molecular level, a central role will be played by chiral synthons, many of which can be made only by biocatalysis."

One biotransformation described at the conference was that of L-carnitine, which is finding new markets as a slimming aid and dietary supplement for athletes in addition to its well-established uses as a pharmaceutical (e.g. as a thyroid inhibitor). The annual demand worldwide is now some 300 tons. As reported by Claude Chassin, Basel-based Lonza has developed a process in which a *Rhizobium* strain (produced by con-

ventional mutation and selection) makes L-carnitine by hydroxylating γ -butyrobetaine with remarkable stereospecificity.

A 0.5m³ continuous culture process has run for over 700 hours without infection. Downstream processing presented problems, however, because it proved difficult to separate the 90 percent L-carnitine from the 10 percent unreacted γ -butyrobetaine. As compared with Lonza's previous method of chemical synthesis, cost savings thus were largely offset by the additional purification. This led the company to experiment with batch cultures. Although these have proved three to four times less productive, the biotransformation is much more efficient. With scale-up work still continuing, Chassin and his colleagues have been running a 2.5m³ fermentor regularly and achieving conversions of over 99 percent.

Chris Evans of Enzymatix (Cambridge, U.K.) described several biotransformations developed to generate multikilogram quantities of chiral synthons. One is the production of unnatural phospholipids that are now

beginning to be used as artificial lung surfactants for the treatment of premature babies. The process is based on the attachment of novel side chains to the glycerol backbone and the transesterification of various bioactive compounds to replace choline as the natural polar head group. Other innovations include a whole cell dioxygenase system to manufacture a wide range of functionalized-cis-dihydrodiols from aromatic feedstocks, and a "uniquely and highly efficient" means of producing optically active bicyclic gamma lactams and the corresponding chiral amino acids.

Stereospecific dehalogenation is another biotransformation technology, developed recently by ICI Biological Products (Cleveland, U.K.) as part of its business of supplying optically active intermediates to the pharmaceutical and agrochemical industries. Mike Nicholds described the use of a *Pseudomonas putida* strain to produce S-2-chloropropionic acid for use in herbicide manufacture, from racemic 2-chloropropionic acid. The process has now reached commercial scale.

—Bernard Dixon