

## SIM MEETING

# THE HUNT FOR MICROBIAL IMMUNE MODIFIERS

BOSTON—"Immune potentiators will become to disease control what antibiotics are today: a ready arsenal of anti-infective weapons for maintaining health." Thus Paula Myers-Keith, quoting a colleague, opened the first session of the Society for Industrial Microbiology's annual meeting here. (Keith is manager of microbiology for International Minerals and Chemical Corp. of Terre Haute, IN, which sponsored the opening symposium.)

Researchers from France, Japan, and the U.S. described immune modifiers derived from, or analogous to, microbially produced metabolites or structural peptidoglycans. These immune modifiers are used to arouse the immune system with endotoxin-like compounds, stimulate macrophage growth with minimal adjuvant units, or a combination of the two. The reported effects include greatly enhancing antibiotic activity, stimulating enduring natural immunity to tumor cells, and greatly increased antibody titers.

The cast of chemical characters is complex: from the whole cells of Freund's adjuvant to mycobacterial cell wall skeletons, to muramyl dipeptide (a generic term embracing hundreds of synthetic analogs of the cell wall's natural N-acetyl muramic acid). Other players include trehalose dimycolate (an intermediate in cell-wall biosynthesis), FK156 (a metabolite of *Streptomyces olivaceogriseus* that structurally resembles muramyl dipeptide), and bestatin (an immune-stimulating metabolite of *S. olivoreticuli*).

Finally, some of the researchers have been tinkering with bacterial endotoxin to eliminate its toxicity while retaining its potent ability to provoke immune responses. Edgar Ribí (Ribí ImmunoChem, Hamilton, MT) outlined recent research on acid hydrolysis of the bacterial endotoxin. This produces an active monophosphoryl lipid A—a precise duplicate of natural endotoxin's lipid portion. Oil-in-water emulsions of monophosphoryl lipid A—with either cell wall skeletons or a muramyl dipeptide-trehalose dimycolate combination—have produced near 100-percent cure rates in guinea pigs with induced tumors, without producing lethargy, toxic shock, or other endotoxin effects. This builds on work (some incorporated in veterinary products on the market) with combinations of cell-wall skeleton and trehalose dimycolate. Injected into equine sarcoid and

bovine cancer eye tumors, this combination has produced striking regression in virtually all equine sarcoid tumors and all but the largest cancer-eye lesions.

Claude LeClerc and Louis Chedid (Institut Pasteur, Paris) are studying others of the "hundreds of [muramyl dipeptide] analogs now available." LeClerc reported massive (i.e. five hundred-fold) increases in tetanus-toxin antibody titers when murabutide was present in challenged mice.

Fujisawa Pharmaceutical Co. (Osaka) has undertaken an innovative double-barreled microbe-screening program. In addition to screening for antibiotics (especially those that impair bacterial cell wall structures), the laboratories are screening for immunomodifiers. In the process, they discovered FK156, a lactyl tetrapeptide. Fujisawa's investigators then constructed an even more potent FK-565 [a heptanoyl- $\gamma$ -D-glutamyl- $\alpha$ , $\epsilon$ -diaminopymethyl(L)-D-alanine]. Kunio Nakahara reported that the latter is effective when administered orally, and its effects last longer than other immune modifiers—providing a measure of protection against even

influenza and herpes viruses.

Another screening program, undertaken by Hamao Umezawa's lab at the Institute of Microbial Chemistry (Tokyo) working with researchers at Nippon Kayaku, yielded bestatin, a compound that inhibits enzymes that attach to the cell surface membrane—enzymes like amino peptidases, alkaline phosphatases, and esterases. Bestatin ([ (2S, 3R) - 3 - amino-2-hydroxy-4-phenyl] butyryl-L-leucine) appeared to reduce both the number and volume of carcinogen-induced gastric tumors in rats by some 78 percent. The compound also appeared to increase interleukin-1 titers in macrophage cultures (with Con A present) some 500 percent. Bestatin has undergone Phase III tests on human patients with malignant skin tumors (*Japan J. Cancer Chemotherapy*, 12: 77-85).

*The complete text of these and other papers presented at SIM's annual meeting will be published in the society's Developments in Industrial Microbiology and the forthcoming Journal of Industrial Microbiology. Contact SIM, P.O. Box 12534, Arlington, VA 22209-8534.*

—Douglas McCormick

## BIOMASS CONVERSION

## U.K.'S BIOTECHNICA LANDS U.S. LANDFILL DEAL

LONDON—Experience gained in increasing gas flow from the Greater London Council's Aveley landfill site for use by Thames Board Mills has helped BioTechnica Ltd. (BTL) secure a contract for similar work with the Delaware-based Methane Development Corp. (MDC). A subsidiary of Brooklyn Union Gas, MDC operates the Fresh Kills site in Staten Island, New York.

Under the arrangement, BTL will develop rapid assessment technologies for predicting gas productivity and yield from new landfills. After pilot work in both countries, the company is to grant MDC an exclusive license covering use and marketing of the procedures within the eastern United States.

BTL's £110,000 (\$150,000), three-year assignment at Aveley has been to devise means of boosting the breakdown of lignocellulosic and other substrates in the anaerobic bioreactor comprising the landfill site. The company isolates the relevant organisms, cultures them artificially, and re-in-

troduces them into the landfill. Genetic manipulation may be employed to increase their activity even further.

BTL was established in 1984 as an affiliate of U.S.-based BioTechnica International (Cambridge, MA). At that time, it raised an initial £1.9 million (\$2.7 million) from its merchant bank, the English Association Trust. Since then, the company has followed a range of environmental and agricultural interests. In order to protect microbial inoculants—which are being introduced for various applications—the company's research director, Howard Slater, evolved a unique fingerprinting technique (see *BioTechnology* 3:393, May '85) for which patent applications have been filed. Over the past year, BTL has produced and sold over 30 tons of a silage inoculant, Super-Sile Plus, worth around £500,000 (\$700,000). The company also has a strong interest in the development of mycorrhizal fungi, and in the idea of introducing novel functions into consortia of organisms.

—Bernard Dixon