JAPAN ROUNDUP

Professor Fumio Yamauchi (Tohoku University, department of food chemistry) has developed a new, low-cost high performance bioreactor for producing low-molecular-weight peptides from *Aspergillus oryzae*. This fungus, which is widely used in Japan for brewing miso (bean paste) and shoyu (soy sauce), is known to have high protease activity.

Conventional bioreactors for protein degradation usually consist of proteases fixed on substrates such as ion-exchange resins, but such systems have proven to be inefficient. The new system uses isolated cell walls from the hyphae of cultured fungi, embedded in agar gel beads. The protease activity is more than two-fold greater than that of conventional systems. Further, the new bioreactor can be used repetitively, reducing operating costs. This system is expected to be useful for commercializing low-molecular-weight peptides in pharmaceuticals and foods; there may also be agricultural applications.

Trying to catch up to U.S. and European research efforts in this field, the Ministry of Agriculture, Forestry, and Fisheries will launch a long-term research project on the genome structure of crops and commercially important animals. The project aims to establish the proper scientific background for applying biotechnology to food production, such as the development of improved strains with favorable phenotypes including disease resistance and high nutrient content. The project is divided into three periods: the first, which will start in the next fiscal year, will focus on sequencing the entire genome of rice; the second, on crops and trees; and the third, on livestock and important aquatic organisms. Each period is expected to be 7 to 10 years; with a total budget of 20 to 30 billion yen, this is the Ministry's largest research project to date. National research Institutes are involved in the project, together with industrial and academic sectors. The establishment of a new research center is also being considered.

Yasuhiko Komatsu's research group (Fermentation Research Institute of the Agency of Industrial Science and Technology) has isolated a pressure-resistant yeast strain. This strain will be used as a model system for studying cellular responses to environmental stresses. Potentially, the yeast may

become the host system for high-pressure fermentations.

The scientists discovered these yeast while studying heat-shock-induced pressure resistance. They isolated naturally pressure-resistant yeast from wild strains that can survive up to 1,500 atmospheres. MRI studies revealed that the strain's membrane fluidity was lower than the wild type; the underlining mechanisms seem to be novel. The results were presented at the International Congress of Heat Shock held in Italy this September.

Combining techniques of synthetic organic chemistry with genetic engineering may prove to be an efficient approach to the development of artificial enzymes. Kenji Soda's research group at Kyoto University Institute of Chemical Research has succeeded in producing an analog of a natural enzyme—heat-resistant glutamic oxaloacetic transaminase (GOT)—by substituting the crucial amino acid and then modifying the enzyme chemically. The researchers substituted cysteine for the essential amino acid lysine; this abolished the enzyme's activity. They then treated it with an ethyleneimine agent. This treatment restored up to 20 percent of the enzyme's activity.

These results indicate that various analogs of natural enzymes, which may have unique functions, can be produced by such a procedure. The research group intends to analyze the structure of the variant GOT, as well as try to improve its resistance to heat, acid and/or alkaline agents, and organic solvents by chemical modification.

The Marine Biotechnology Institute will launch joint research projects with the Woods Hole Oceanographic Institute (WOI), the Australian Institute of Marine Science (AIMS), and the USSI Heliosynthesis Laboratory (France). The research areas include thermal-resistant bacteria found in the waters around hydrothermal vents (with WOI), CO₂ fixation by calcareous algae and the mechanism of symbiosis between the algae and corals in the Great Barrier Reef (with AIMS), and microalgae with high potential CO₂ fixation (with USSI).

The Marine Biotechnology Institute is an R&D company specializing in marine organisms; it was established with the support of 24 companies as well as the Agency of Industrial Sci-

ence and Technology. The two facilities in Kamaishi (Miyagi Prefecture) and Shimizu (Sizuoka Prefecture) started research in July, and a research vessel is also operating. The Institute is expected to play an important role in facilitating international research cooperation.

Collaborative research between groups at Sumitomo Chemical (Osaka), the Calpis Food Industry (Tokyo), and Hokkaido University has produced a drug that can kill more than 90 percent of human immunodeficiency virus (HIV)-infected cells *in vitro*. The compound consists of CD4 protein—provided by Calpis and Hokkaido University—incorporated into Sumitomo's liposomes.

Sumitomo will soon launch preclinical animal toxicity experiments and start clinical trials in the U.S. in cooperation with NIH and Harvard University. The researchers predict that the new drug may be on the market within four to five years.

Takeda Chemical Industries (Osaka) and Sumitomo Chemical have independently made formal objections to the Japan Patent Office concerning the validity of a patent application from the University of California and Japan Pharmaceutical Development (Osaka). The application includes the use of human monoclonal antibodies in cancer therapy, but extends this coverage to all human monoclonal antibodies. The Patent Office gave public notice last December, and the patent would have issued in six months if there had been no formal objection.

Takeda has been developing human monoclonal antibodies as a hepatitis B vaccine, and advocates that the patent is invalid because information about the B cells used to make the hybridoma has already been published in scientific papers and thus is a matter of common knowledge. Sumitomo's claim is based on similar logic. Japan Pharmaceutical Development, however, insists that the patent has already issued in 10 countries and there is no reason for it to be rejected in Japan.

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