New Therapeutics Through Fermentation Technology

Applications of microbial fermentation technology in new therapeutics are expanding. SAFC offers unique cGMP fermentation-based manufacturing capabilities through its Jerusalem facility, including highly potent APIs and biologics. SAFC scientific teams provide a complete range of services, including process evaluation and development, optimization and scale up, technology transfer, manufacturing, analytical testing and regulatory filing to help customers bring new drugs to market faster.

SAFC is finding new applications for its expertise in fermentation technology, including the synthesis of high potency active pharmaceutical ingredients (HPAPIs) and therapeutics. These applications draw on the use of microbial biofactories, which offer the pharmaceutical industry a diverse, reliable, powerful, and economic source for therapeutics, many of which are primarily isolated through microbial fermentation.

**Chemical Therapeutics**
Toxic, small, organic molecules produced naturally by microorganisms in response to stress are called secondary metabolites. They are used in cancer therapy and in the treatment of infectious diseases.

**Cancer Therapy:** Various HPAPI antibody–drug conjugates (ADCs) are currently in clinical trials. Some are gaining FDA approval for difficult-to-treat indications, mainly in the treatment of cancer. Wyeth’s FDA-approved Mylotarg® ADC is a recombinant humanized IgG4 kappa antibody conjugated with a cytotoxic antitumor antibiotic, calicheamicin, which is isolated through the fermentation of a bacterium, *Micromonospora echinospora* subspecies *calichensis*. Genentech’s trastuzumab-dM1 is an ADC of ImmunoGen’s DM1 agent linked to Genentech’s humanized anti-HER2 antibody, trastuzumab (Herceptin®, approved to treat breast cancer). DM1 is a proprietary derivative of a naturally occurring substance belonging to the ansamycin family of secondary metabolites and is isolated through fermentation of an *actinomycyes* species, *Actinosynnema pretiosum*.

**Treatment of Infectious Diseases:** Many antibiotics are sourced from living microorganisms, used either in their natural state or (in the case of semisynthesis) chemically modified. Aminoglycosides are produced and isolated from bacteria of the *Streptomyces* genus, used in their existing form to provide drugs such as streptomycin (a bactericidal agent) and Hygromycin B (a killer of bacteria and fungi). Doxycycline is a semisynthetic tetracycline. Tetracyclines were isolated from Streptomyces subspecies such as *aureofaciens* and *rimosus*. Doxycyclin was developed in the 1960s by Pfizer and marketed under the Vibramycin® brand name.

**Biological Therapeutics**
Fermentation-derived biological therapeutics are used in a wide range of medical indications.

**Native Proteins:** Collagenases are a group of enzymes produced by the bacterial pathogen *Clostridium* genus. Native isolated collagenases are used in a variety of medical indications involving collagen disorders, including Santyl® ointment and Iruxol® for the removal of dead skin from wounds and burned areas in poorly healing wounds and necroses, as well as Xiafles Dupuytren’s contracture, a condition resulting in the contracture of the fingers into the palm. Other collagenases are currently in clinical trials for indications including frozen shoulder, cellulite, and lipomas.

**Recombinant Proteins:** Manufactured in various heterologous microbial hosts, mainly bacteria, these include *Escherichia coli*, *Pseudomonas fluorescens* and yeast (*Pichia pastoris*). Recombinant Lysostaphin has been investigated in various models for infections caused by a *Staphylococcus aureus*, either systemic or specific, such as endocarditis (inflammation of the inner layer of the heart). Recombinant fibroblast growth factor has been implemented in various disorders, including angiogenesis in limb ischemia, tissue regeneration, cartilage injuries, wound healing, and remodeling of bone and cartilage. Antibody fragments are small portions of full-length antibodies sufficient to confer therapeutic activity. Fragment production with microbial systems has been demonstrated with *E. coli*, yeasts, and fungi. Various companies have antibody fragments under development.

In addition to advanced fermentation capabilities, SAFC offers a range of contract manufacturing services including bioconjugation, viral vectors and vaccines, protein extraction and purification, and high-potent manufacturing. To learn more, visit www.safcpharma.com.

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