APPLIED BIOSYSTEMS MERGES

Applied Biosystems (AB, Foster City, CA) and **Perkin Elmer** (Norwalk, CT) entered into a merger agreement under which Perkin Elmer will exchange 0.678 shares of its stock for each share of AB's stock. The merger has been approved by both companies' boards of directors, yet still requires approval by shareholders and certain regulatory bodies. At current market prices, the transaction is valued at approximately $330 million.

AB also completed a $13 million first round financing for its subsidiary, **Lynx Therapeutics**, with **Chiron** (Emeryville, CA). In the transaction, AB received 10 million shares of Lynx series A preferred stock for $10 million, and Chiron received 1.5 million preferred shares for $1.5 million. The development collaboration between Lynx and Chiron focuses on antisense therapeutic drugs aimed at three viral targets, namely hepatitis B, hepatitis C, and HIV. At the same time, AB will spin off Lynx into an independent company.

Finally, AB and **Ribozyme Pharmaceuticals** (Boulder, CO) agreed to collaborate on large-scale synthesis of RNA for use in Ribozyme's commercial development of ribozyme technology. The companies have established a long-term supply/equipment agreement in the field of RNA chemistry that will involve an acceleration in the large-scale synthesis of RNA.

•**Eli Lilly** (Indianapolis, IN) granted an exclusive license to **Oclassen Pharmaceuticals** (San Rafael, CA) to distribute Lilly's Cordran, topical corticosteroids for treatment of skin inflammation, and Cinobac, an oral quinolone antibiotic for treatment of urinary tract infections.

Lilly also agreed to acquire an equity stake in **GenPharm International** (Mountain View, CA) as part of a cooperative venture seeking cancer treatments. The companies plan on developing human monoclonal antibodies for use in treating certain cancers. The antibodies will be generated from GenPharm's transgenic mouse strain containing human antibody genes. These antibodies will be used in conjunction with Lilly's drug-targeting technology.

Furthermore, Lilly and **NeXagen** (Boulder, CO) signed a collaborative agreement to develop pharmaceuticals directed against two molecular targets involved in certain cardiovascular and inflammatory disorders.

•**Ciba-Geigy** (Basel, Switzerland) and **Sibia** (La Jolla, CA) have entered into a collaborative research agreement on the use of cloned human excitatory amino acid receptors to identify and develop drugs for central nervous system diseases. Disease targets include stroke, epilepsy, and neurodegenerative diseases such as Alzheimer's.

Ciba also reached an agreement with **Incyte Pharmaceuticals** (Palo Alto, CA) resolving a U.S. patent interference regarding a protease inhibitor, Protease Nexin-1 (PN-1), derived from platelet granules. Incyte is developing PN-1 as a therapeutic for treatment of inflammatory and degenerative disorders. The interference, declared in July, 1991, concerned pending patent applications covering the PN-1 cDNA and recombinant methods of production. Under the terms of the agreement, Ciba will assign its worldwide DNA patent rights and related know-how to Incyte in exchange for a royalty on product sales.

•**Cambridge Biotech** (Cambridge, MA) signed licensing agreements with **SmithKline Beecham** (Philadelphia, PA) and with **Genentech** (S. San Francisco, CA) for use of its QS-21 adjuvant, Stimulon, in their vaccines. SmithKline plans to use Stimulon in more than 25 vaccines targeted at viral hepatitis conditions, Lyme disease, AIDS, herpes, and influenza. Genentech plans to use Stimulon in its gp120 AIDS vaccine.

•**Genetics Institute** (GI, Cambridge, MA) sold its minority interest in **WelGen** (W. Greenwich, RI) to the majority partner, **BW Manufacturing**, a **Burroughs Wellcome** (Research Triangle Park, NC) subsidiary. WelGen will operate under the name "BW Manufacturing," and will be a wholly owned subsidiary of Burroughs Wellcome. Some of Wellcome's alpha interferon product, Wellferon, is manufactured at the plant. Wellferon is a treatment for hairy cell leukemia and chronic hepatitis B in a number of countries.

GI also signed a limited exclusive collaboration and licensing agreement with **Genetic Therapy** (Gaithersburg, MD) to commercialize Factor VIII and Factor IX gene therapy products using viral vector systems. Both factors are proteins essential to normal clotting, and are missing or defective in patients with hemophilia A, the most prevalent form of hemophilia, and hemophilia B, a rarer form of hemophilia.

•**Ligand Pharmaceuticals** (San Diego, CA) and **Glaxo** (Research Triangle Park, NC) have established a collaborative research program to discover and develop drugs to treat or prevent atherosclerosis, a disease characterized by the formation of fatty plaques in the walls of arteries that often lead to heart attacks or strokes. The effort combines Ligands's hormone-activated intracellular receptor technology with Glaxo's research and development capabilities and international marketing structure.

Ligand also agreed to collaborate with **E. Merck** (Darmstadt, Germany) on a drug discovery and development program that involves Ligand's screening of a key segment of E. Merck's compound library.

•**NeoRx** (Seattle, WA) and **Boehringer Ingelheim** (BI, Ingelheim, Germany) completed their alliance. As part of the agreement, NeoRx received $8 million for BI's purchase of two million shares of NeoRx common stock. The agreement involves BI receiving worldwide manufacturing and marketing rights outside the U.S. to NeoRx's OncoTrac products, while NeoRx keeps U.S. marketing rights.

Also, NeoRx and **Sterling Winthrop** signed a definitive agreement that gives Sterling a non-exclusive license to use certain of NeoRx's technology for labeling antibodies and other targeting proteins with therapeutic radiometals for cancer therapy. NeoRx also granted to Sterling exclusive rights to certain antibodies for use in radioimmunotherapy of cancer, and non-exclusive rights to these antibodies for other forms of cancer therapy.

NeoRx, furthermore, teamed with **Organon International** (Oss, the Netherlands) to begin a clinical trial of a colon cancer therapy product. The trial will assess the combined use of NeoRx's rhenium radiotherapy technologies and Organon's completely human monoclonal antibodies currently under development as cancer therapeutics.

•The second part of a long-running dispute between **Amgen** (Thousand Oaks, CA) and **Ortho Pharmaceutical** (New Brunswick, NJ) has been settled. A private arbitrator found that Ortho defaulted on its contractual obligation to

develop and register Amgen's hepatitis-B vaccine and interleukin-2 products, under terms put forth in a 1985 marketing agreement with Amgen. It is expected that Amgen will now receive an approximately $90 million award, a sum that substantially reduces the $164 million that Amgen was ordered to pay Ortho after the first part of the case was decided in June, 1991.

•**Syntex Pharmaceuticals** (Palo Alto, CA) terminated an agreement with **Greenwich Pharmaceuticals** (Fort Washington, PA) for the companies to develop and co-market Greenwich's arthritis drug Therafectin. Under the 1989 agreement, Syntex had "co-exclusive rights" to make and sell the drug in the U.S., and exclusive rights to market the drug in Canada, Mexico, the Bahamas, and Australia.

•**Procter & Gamble** (P&G, Cincinnati, OH) will develop and use a new cultured human tissue test to help insure the eye safety of its new products and ingredients. The test uses a technology invented by **Advanced Tissue Sciences** (ATS, La Jolla, CA). Procter & Gamble will grant worldwide license rights to ATS, enabling it to build P&G's new test procedure into its screening kits for sale to other manufacturers.

•**Abbott Laboratories** (Chicago, IL) is swapping blood products for **North American Biologicals** (Miami, FL) stock. Abbott will receive 2 million shares, or a 16 percent stake in North American, and will hand over exclusive rights to hepatitis B immune globulin, which is used to prevent people exposed to hepatitis B from coming down with the disease. North American will also receive rights to Abbott's experimental HIV immune globulin, a controversial product.

•**Scotgen** (Aberdeen, Scotland) and **Nissin** (Osaka, Japan) have entered into a collaboration to develop an immunotherapeutic against HIV. Nissin has isolated a mouse monoclonal antibody that, in the laboratory, neutralizes a range of isolates of HIV. Scotgen will use its technology to convert the mouse antibody into a human antibody before clinical trials.

•**Genentech** is discontinuing its partnership agreement with **Telios Pharmaceuticals** (San Diego, CA) on a drug for treating various thrombotic conditions. In the January, 1991 agreement, Telios granted most worldwide rights to Genentech for its TP-9201, a drug designed to treat heart attacks and other cardiovascular conditions due to abnormal blood clotting. Telios retained rights to the drug in the Far East. Telios now has exclusive worldwide rights to the drug.

Genentech also concluded an agreement with **Univax Biologics** (Rockville, MD) to jointly develop an antibody-based therapeutic with the potential to prevent and treat HIV-1 infections. The approach is based on Genentech's gp120 vaccine and on Univax's expertise in developing hyperimmune immunoglobulins for intravenous administration.

•**Cell Genesys** (Foster City, CA) signed a collaborative agreement with **Bio-Technology General** (BTG, New York) in which Cell Genesys will develop T cell transplant products for treatment of cytomegalovirus (CMV) infection, a potentially life-threatening infection in patients with immunodeficiency disease. The agreement grants Cell Genesys exclusive worldwide license to BTG's anti-CMV antibodies for the development of T cell transplant products for treatment of CMV infection. BTG will receive licensing fees and royalty payments.

Cell Genesys granted **TSI** (Worcester, MA) a non-exclusive license to use gene targeting technology for the development of genetically modified animals as models of human disease. The license provides access for commercial purposes to Cell Genesys' proprietary technology.

•**Glycomed** (Alameda, CA) and **Alza** (Palo Alto, CA) reached an agreement in principle to develop one or more products incorporating an implantable, controlled-release drug delivery system that may be useful in patients who undergo open heart surgery and other procedures. The first products to be developed will address thrombosis, vessel closure due to clotting, and restenosis, vessel closure due to smooth muscle cell growth, in blood vessels following coronary artery bypass surgery.

•**Gensia Pharmaceuticals** (San Diego, CA) has acquired from **Intavent** exclusive U.S. distribution rights to the laryngeal mask airway (LMA), a product for maintaining an open airway in surgical patients receiving general anesthesia. The LMA is designed to provide an alternative to a face mask or an endotracheal tube.

•**Immune Response** (San Diego, CA) signed a letter of intent to acquire **TargeTech** (Meriden, CT) for $3 million and 1.3 million shares of Immune Response stock. The proposed transaction has an indicated total value of $20.7 million.

•**Emisphere Technologies** (Hawthorne, NY) has entered a research collaboration with **J³Biologics** (New York) to study the feasibility of developing an oral formulation of Factor IX to treat hemophilia B. Factor IX is a protein essential to normal clotting that is missing or defective in people with hemophilia B. It is currently administered only intravenously.

•**ImmuCell** (Portland, ME) sold stock and stock options to **Cambridge Biotech**. The companies plan to collaborate on the use of passive immunotherapy for treatment of human disease and in the development of animal health products.

•**Agouron Pharmaceuticals** (San Diego, CA) will collaborate with **NeXagen** and **Selectide** (Tucson, AZ) in a program to discover new drugs for treatment of AIDS. Each company will bring proprietary technologies to bear on discovery of chemical compounds that block reverse transcriptase, an enzyme required for replication of HIV.

•**Celtrix** (Santa Clara, CA) has signed a definitive agreement to acquire **Baltimore Biotech**, a privately held company focused on treatment of ophthalmic diseases. Under the terms of the agreement, Baltimore Biotech will become part of Celtrix's ophthalmic research and development team. All outstanding Baltimore Biotech stock will be exchanged for newly issued shares of Celtrix common stock.

•**Alanex Laboratories** and **Tanabe Research Laboratories**, both in San Diego, CA, agreed upon a research collaboration to design and develop pharmaceuticals for treatment of immuno-inflammatory disease. Alanex will apply its molecular design technology to identify the three-dimensional pharmacophores of peptide molecules. Tanabe will provide two chemical databases to aid in the identification of the pharmacophores.

•**Allelix Biopharmaceuticals** and **Nordion International**, both in Toronto, Canada, have established **Resolution Pharmaceuticals** to develop and manufacture radioisotopically labeled peptides to diagnose disease. Financial terms of the deal were not disclosed.

•**Advanced Tissue Sciences** (ATS) has acquired **Neomorphics**, a company focused on engineering human organs and tissues for transplantation. Under terms of the agreement, all of Neomorphics' stock will be exchanged in two installments for ATS common stock valued at $21 million. ATS retains the right to pay for any portion of the purchase price in cash.

•**Quidel** (San Diego, CA) has established a joint marketing and distribution venture with **Epignost**, one of its major European distributors based in Austria. The new company, **Quidel/Epignost Ventures** (Linz, Austria), not only establishes a Quidel presence in Europe, but will focus on the expanded marketing and distribution of all Quidel and Epignost products into new territories within Europe and the Middle East.

•**Ecogen** (Langhorne, PA) signed a three-year, $9.5 million biopesticide research agreement with Italy's **3A**. Part of the funding will be used for the development of formulations and fermentation

processes for Ecogen's biofungicide products for the control of powdery mildew on plants and post-harvest rot on fruits and vegetables. The funds will also be used for development of nematodes, small roundworms that control insects in soil and plant systems.

Ecogen also completed its acquisition of the pheromone business of **Scentry**. The pheromone-based products use natural odors emitted by insects for a variety of agricultural applications. Pheromones can be used alone or in conjunction with pesticides to control insect populations.

•**Agracetus** (Middleton, WI) reached an agreement with **Monsanto** (St. Louis, MO) to use Agracetus technology in the development of insect-protected cotton, corn, and tomato. The technology includes an insect crystal protein gene isolated from *Bacillus thuringiensis* (*B.t.*), and Agracetus technology required to make the *B.t.* gene function effectively in plants. Specific terms of the agreement were not disclosed.

•**Embrex** (Research Triangle Park, NC) has entered into a leasing and licensing agreement with **Tyson Foods** (Springdale, AR). The agreement stipulates that Tyson Foods will fully convert one of its poultry hatcheries to incorporate two of Embrex's *in ovo* injection systems. Financial terms were not disclosed, but Tyson Foods does have the opportunity to convert additional hatcheries over a five-year period.

•**Calgene** (Davis, CA) agreed to become the exclusive supplier of vegetable-oil-based environmental awareness lubricants (EAL) for **Mobil Oil**. Under the agreement, Calgene's subsidiary **Calgene Chemical**, will produce Mobil's proprietary lubricants and supply the formulated product to Mobil. The EAL products are functionally equivlent to petrochemical based lubricants, but they have a rapeseed oil base and a carefully formulated additive package making them fully biodegradable.

•**Applied Immune Sciences** (Menlo Park, CA) signed a partnership deal with **Innovet** (W. Palm Beach, FL) to help livestock farmers selectively breed male or female animals by adapting medical cell-separation technology. Genders can be chosen by employing fluorescence-activated cell sorting machines that use mouse monoclonal antibodies to seek out and bind to cell surface markers to help pick out male or female sperm.

•**Hoechst Celanese** (Somerville, NJ) sold its remaining 15 percent stake in **Celgene** (Warren, NJ). Hoechst does not usually hold minority positions in companies.

REGULATORY

GensiaPharmaceutical's (San Diego,

CA) heart surgery drug Arasine has had mixed results in clinical trials so far. Tests conducted in the U.S. show positive and significant benefits in reducing the incidence of heart attacks and other adverse outcomes from heart bypass surgery. But data in Canada and several European countries were not statistically significant. Gensia's stock market value fell by more than one-third when this information was disclosed; shares closed at $22, down $13.7. Five of the company's shareholders have filed a suit against Gensia, claiming that company insiders knew of the disappointing trial results and were selling their own stock before the public notice.

•**Schering-Plough** (Madison, NJ) and **Sandoz Pharma** (Basel, Switzerland) have received approval from the European Community's (EC) **Committee for Proprietary Medicinal Products** (CPMP) for their jointly developed Leucomax, a granulocyte macrophage colony-stimulating factor. Leucomax was approved for chemotherapy-induced neutropenia in cancer patients, to accelerate recovery after autologous bone marrow transplant, and to combat gancyclovir-induced neutropenia in AIDS patients with cytomegalovirus retinitis. Each of the 12 countries within the EC will now decide whether to allow the drug to be marketed in their countries.

•**U.S. Bioscience** (W. Conshohocken, PA) has submitted a marketing application to the CPMP for its drug designed to treat side effects of cancer chemotherapy, Ethyol. Shares in the company rose to $10.4 with the news; the stock had nosedived earlier in the year when the outlook for approval of Ethyol in the U.S. became clouded.

•**Genzyme**'s (Cambridge, MA) Ceredase, an orphan drug for treatment of Gaucher's disease, is under fire for outrageous pricing. Congress' **Office of Technology Assessment** (OTA, Washington, DC) issued a report about Ceredase, saying the per year cost of the drug would force recipients to exhaust all their insurance benefits for two or three years' worth of the drug. Genzyme has said it would provide Ceredase free of charge to those people who had used all their insurance benefits, but OTA asserts that is too little, too late. Genzyme says that the price of the drug is high because it is expensive to make.

Results of phase I/II clinical studies of Genzyme's Thyrogen, recombinant human thyroid stimulating hormone (TSH), demonstrated that it is safe to expand the clinical trials to phase III, involving a larger patient population and a dosage regimen for detection of thyroid cancer through radioiodine whole body scanning. The use of rhTSH may enable patients to continue taking thyroid hormone supplement prior to and during diagnostic testing, and thus avoid the debilitating symptoms of hypothyroidism such as weakness, weight gain, lethargy, and depression. Genzyme has received orphan drug designation for Thyrogen.

•Synvisc, made by **Biomatrix** (Ridgefield, NJ) for treatment of osteoarthritis, is now available in Canada. Sunvisc, a chemically modified version of naturally occurring hyaluronan, has been shown in studies in Europe and Canada to significantly lessen the pain and increase the mobility of an arthritic joint immediately following and up to six months after the treatment in the majority of patients treated.

•The joint venture of **Chiron** and **Ciba-Geigy**, **Biocine**, has conducted tests with its herpes simplex type 2 virus vaccine showing the vaccine to be safe and effective. The gene-spliced vaccine uses a proprietary adjuvant called MF59 that employs microscopic drops of oil to heighten stimulation of the immune system.

•**Gynex Pharmaceuticals** (Vernon Hills, IL) began phase III clinical study of its drug Androtest-SL, sublingual testosterone, for treatment of men with hypogonadism, low testosterone levels. This condition is associated with impotence, insufficient muscle development, and bone loss. Gynex believes Androtest-SL is preferable to injectable testosterone because of its ease of administration, and because the drug may allow physicians to better individualize a patient's therapy since it is given daily instead of every two to three weeks as are injectable products.

•**Immunomedics** (Morris Plains, NJ) initiated phase III trials of its infectious disease imaging agent, ImmuRAID-MN3, for finding the location and extent of suspected infections affecting prosthetic joints, bones, and foot ulcers in diabetic patients. ImmuRAID-MN3 consists of an antibody fragment labeled with the radioisotope technetium-99m. Upon injection into the patient, the radiolabeled antibody fragment seeks out and attaches to granulocytes. A standard nuclear medicine camera is used to locate the resulting radioisotope concentrations within the body, pinpointing the site and extent of infection.

•Results of **Imutec**'s (Toronto, Ontario, Canada) phase II study of Virulizin in patients with pancreatic cancer showed that the drug produces no toxic side effects. Virulizin is currently undergoing phase II trials for pancreatic, malignent melanoma, kidney, stomach, and recurrent rectum and colon cancers. The drug's specifications were not released.

•**Organogenesis** (Canton, MA) has presented data from clinical trials of its Graftskin for burn wounds. Graftskin, a full-thickness living skin equivalent containing both the dermal and epidermal layer of the skin, causes no immune reaction or adverse response in humans. The study also indicates that Graftskin improves wound healing, looks and feels like human skin, conforms to the wound bed, and can be stapled or sutured to the wound site. The **Food and Drug Administration** (FDA, Bethesda, MD) has approved the company's supplemental investigational device exemption to begin trials using Graftskin to treat chronic skin wounds resulting from venous stasis disease.

•**Cephalon** (W. Chester, PA) has completed phase I trials of Myotrophin, the company's compound for treatment of amyotrophic lateral sclerosis and peripheral neuropathy. The data revealed that Myotrophin, recombinant human insulin-like growth factor-1, administered by daily subcutaneous injection produced no significant side effects and was well tolerated in healthy volunteers.

•**Bio-Technology General** started phase II studies of its human growth hormone (hGH) in pancreatic cancer patients. The hormone is to be used to prevent or treat cachexia, a wasting syndrome, in pancreatic cancer patients. The company is currently conducting additional clinical studies aimed at assessing the utility of hGH in treatment of cachexia in HIV patients, and in the prevention of muscle atrophy in elderly patients hospitalized with hip fracture.

•**Glycomed** (Alameda, CA) has completed phase I trials of Galardin MPI, its product for treating corneal ulcers, a severe sight-threatening disease. Galardin MPI was shown to suppress the action of enzymes that attack carbohydrate-protein complexes and other components of the cornea's support structure. The phase I studies showed that the treatment was safe and tolerable at various dose levels.

•Phase I trials of **Sphinx Pharmaceuticals**' (Durham, NC) Kynac for treatment of psoriasis have shown Kynac to be well tolerated in healthy volunteers. The trial also indicated that Kynac, administered as a topical ointment, produced no significant skin irritation and no detectable absorption into the bloodstream. Kynac is designed to inhibit the activity of an intracellular enzyme, protein kinase C, that appears to mediate key cellular functions involved in psoriasis, including inflammation and cell proliferation.

•**Advanced Tissue Sciences** (ATS) had two supplements to its investigational device exemption approved by FDA for Dermagraft, the company's living human dermal replacement. The approval allows ATS to expand its clinical trials of Dermagraft to treat decubitus and diabetic skin ulcers. —**Christine Punzo**