

Chapter 2

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Astrom Biosciences, Inc.

A Patient-Friendly Approach to Human Cell Transplantation

One of the most important recent developments in cancer treatment has been the ability to harvest stem cells from bone marrow or blood to produce blood and immune system cells, and inject them into a cancer patient after drug or radiation therapy. These therapies kill cancer cells, but they also destroy life-protecting stem cells. Reinfusion of harvested stem cells enables the body to regenerate the blood and immune systems in the now cancer-free patient. Preferably, the stem cells come from the patient's own bone marrow. When that is not feasible, they may be taken from another donor.

Serious Drawbacks to Existing Methods

Good as it is, stem cell harvesting has important drawbacks. Harvesting stem cells from bone marrow is painful, usually requiring 100 to 140 needle sticks — performed as major surgery under general anesthesia — to extract from the hip or other large bones enough marrow for successful transplantation. Some cancer patients are not strong enough to withstand so many extractions. A few are so ill they can't afford to postpone therapy while stem cells are being harvested. Still others suffer significant side effects (pneumonia, pulmonary embolism, bone marrow inflammation) from the extraction process itself. A typical procedure involves eight separate donor visits (one for the



Ex Vivo Cell Expansion - From the Lab to the Clinic

extraction, several for blood testing and other medical procedures, one for reinfusion of the stem cells), takes about 16 hours altogether and costs \$10,000 to \$15,000.

Another harvesting method — peripheral blood progenitor cell (PBPC) collection — is in some ways an improvement over traditional bone marrow harvesting. PBPC involves injecting the donor (who might be the patient) with drugs to stimulate the movement of stem cells from the bone marrow into the blood stream. When it becomes enriched with stem cells, the blood is circulated through an apheresis machine, where stem cells are separated, and then back to the donor.

PBPC collection typically involves 21 donor visits (at least one for drug administration, three or four for apheresis, some for blood work, others for follow-up work related to the apheresis, one for reinfusion), takes an average of 39 total hours, requires about 22 needle

sticks and costs around \$16,000. It has gained popularity over bone marrow harvesting in recent years, the company reports. This is particularly true for collecting cells from cancer patients themselves, in part because some patients receiving PBPC-based treatment have less need for platelet transfusion.

The overall costs of cancer treatment where stem cell therapy is used may total \$100,000 or more. These costs include diagnosis, chemotherapy, radiation therapy, stem cell transplant therapy, and patient management. The costs of stem cell transplant therapy include the costs of cell collection, the costs of reinfusing the cells, and patient support during post-transplant recovery. The latter involves hospitalization, antibiotic treatment, infusions of platelets and red blood cells, and management of adverse reactions to large-volume cell infusions.

PROJECT:

To design and construct a desktop-size device that can expand small samples of stem cells, a process that would enable reductions in the risk, pain, time and cost of collecting these specialized blood-production cells for use in bone marrow transplantation for cancer patients.

Duration: 7/1/1992 — 6/30/1994

ATP Number: 91-01-0243

FUNDING (IN THOUSANDS):

ATP	\$1,220	45%
Company	1,514	55%
Total	\$2,734	

ACCOMPLISHMENTS:

Astrom designed, constructed and validated a desktop-size bioreactor to produce large amounts of stem and other cells from bone marrow, umbilical cord blood and possibly other human tissues. A number of signs indicate the value of this accomplishment:

- Astrom received a fundamental patent for its bioreactor:

“Bioreactor for Mammalian Cell Growth and Maintenance”

(No. 5,688,687: filed 6/7/1995, granted 11/18/1997).

- It has applied for several additional patents for technologies related to the ATP project.
- By the end of the ATP award period in June 1994, Astrom staff had published or presented at professional conferences numerous technical papers on the company's AastromReplicell™ Cell Production System (System), which incorporates the Biochamber developed with ATP funds.
- In October 1995, Astrom received \$35 million from Rhone-Poulenc Rorer for use of System technology worldwide for cell and gene therapies involving lymphoid blood cells.
- Astrom raised \$21 million in new investment capital via an initial public stock offering in February 1997.

- In November 1997, when Astrom received the patent listed above, the company's stock price jumped more than 60 percent in one day.

- By the end of 1997, Astrom had entered into agreements with SeaMED and Ethox Corporations and Anchor Advanced Products for the collaborative development and manufacture of certain components of the system.

- To date, the System has been used in clinical trials at six U.S. and two foreign sites with more than 60 patients, and additional trials are under way.

COMMERCIALIZATION STATUS:

Clinical trials are in progress. The firm is also looking for partners with whom to develop a marketing relationship.

OUTLOOK:

There are high expectations that this new technology will be useful in a variety of medical treatments. Test results at various stages in the regulatory process have been promising. The stock market response to the initial public stock offering, patent-grant announcements and attention from investment analysts suggest that the private market believes the company and its technology have a good future. Also, a recent detailed economic study indicates this new technological approach could yield significant social benefits just in treating cancer patients with solid tumors.

COMPANY:

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Dominos Farms, Lobby L
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Number of employees:

4 at project start, 70 at the end of 1997

New Approach Promises Large Benefits

A cell expansion system developed by Aastrom Biosciences could potentially mitigate most of the drawbacks associated with current harvesting techniques while reducing costs and increasing the number of patients who could use Aastrom's procedure. The company was founded in 1989 and had only four persons on staff when it gained ATP support three years later. Wide-scale use of its system would pro-

duce large benefits across the economy via new therapies, reduced treatment costs and lower risks to patients undergoing cell harvesting and transplantation.

Aastrom expects cell harvesting via its AastromReplicell™ Cell Production System — which induces cells to rapidly multiply or expand — will be cost competitive. The typical patient/donor is likely to need just two clinic visits, one for harvesting a small amount of bone marrow and the other for reinfusing the

expanded cells. An average of just seven needle sticks would be required during the initial visit.

The core technology of the system is a bioreactor that expands small amounts of bone marrow into a transplant product rich in stem cells and progenitor cells (stem cells that have started maturing into blood or immune cells). During a single 20-minute outpatient procedure, less than 50 millimeters of bone marrow is extracted from the patient under local anesthesia. The marrow is injected into a disposable cassette — about the size of a large pizza — which is inserted like a video cassette into the automated bioreactor. A key aspect of the system is the creation of culture conditions that duplicate the human bone marrow environment. The cassette uses growth media, oxygen supplies and proprietary processes within the bioreactor to stimulate the marrow to produce its own growth factors. Over 12 days, the cell population expands five to 10 times while

... the cell expansion system ... could eventually mitigate most of the drawbacks associated with current harvesting techniques while reducing costs and increasing the number of patients who could use Aastrom's procedure.

stem and progenitor cells expand even more, producing enough cells for effective transplantation.

Scale-Up and Clinical Trials

Aastrom has successfully scaled up a small laboratory prototype of the cell expansion system to one large enough for clinical use. Clinical research has confirmed that cells produced by this device, called “the System,” can safely be infused into patients.

In the first test of the System, a dose-ranging study with seven lymphoma patients at the University of Michigan Medical Center in 1993,



Injecting into processor.

Astrom found that stem cells generated with its procedure were as safe as those collected by the direct bone-marrow harvesting technique. And in the first feasibility trial of the System — with 10 breast cancer patients at the University of Texas M.D. Anderson Cancer Center in Houston — standard clinical recoveries were seen following injection of the System-produced cells, showing that the System can be operated adequately by clinical personnel.

Another clinical trial, completed in May 1997, reported excellent findings for six breast cancer patients treated through the Bone Marrow Transplant Program at Loyola University Medical Center in Chicago. The study demonstrated that the System technique produced recovery results in line with outcomes for transplantation using other cell harvesting procedures.

Favorable results were also reported at the American Society of Hematology conference in December 1997. A Duke University Medical Center preclinical study showed that the System reduced the number of tumor cells during production. At the same conference, Astrom announced completion of another Loyola clinical study, this one with 19 patients, that generated further evidence that bone marrow grown in the System retained stem and other key immune cells needed to restore vital tissues after drug and radiation therapy.

Another clinical trial, completed in May 1997, reported excellent findings for six breast cancer patients . . .

Intellectual Property and Stock Market Reaction

Protection of its intellectual property has always been important to Astrom. The company was founded as a joint effort between the company's initial investors and the University of Michigan. The investors and the University agreed that inventions by the three principal researchers, all University professors, would be assigned to the University and licensed exclusively to Astrom. In March 1992, prior to the ATP award, Astrom and the University signed

Astrom's policy is to disseminate its findings widely after establishing protections for its intellectual property.

a detailed licensing and royalty agreement. Through the end of 1997, 12 patents covered by the agreement had come out of the Astrom/University of Michigan collaboration. Most of them underlay the ATP-funded technology. News reports about the granting of two of them in September 1997 were immediately followed by a substantial increase in the price of the company's stock.

The company is also pursuing patent protection for inventions not covered by the agreement with the university. In 1997, Astrom received in its own name a fundamental patent — "Bioreactor for Mammalian Cell Growth and Maintenance" — for the System method and device. News that this patent had been granted was accompanied by a one-day increase of 60 percent in the company's stock price.

Astrom's policy is to disseminate its findings widely after establishing protections for its intellectual property. This is true of the technical specifics of its discoveries, as well as the results of clinical trials. Company staff have produced numerous papers for presentation at professional conferences or publication in professional journals.

Strategic Alliances for Commercialization

In 1993, the company entered into a strategic alliance with COBE Laboratories and COBE BCT (collectively, COBE) for the worldwide distribution of the System for stem cell therapy and related uses. COBE committed up to \$20 million in equity investment in Astrom. In addition, Astrom and COBE initiated a clinical trial in France in early 1997 to evaluate the use of System cells to promote the recovery of blood cell production in breast cancer patients undergoing aggressive marrow-damaging chemotherapy. Astrom is seeking approval to market the System in Europe.

In September 1995, Astrom entered into a research and development collaboration with

Rhone-Poulenc Rorer (RPR), granting RPR a right to license the System for lymphoid cell applications. Under the agreement, RPR will invest \$35 million. In September 1997, Aastrom had received \$3.5 million in equity payments and \$1.5 million in revenues from RPR.

Initial Public Stock Offering

In addition to financial support from strategic alliances, the company has secured funding in the public capital market. In February 1997, Aastrom conducted its initial public stock offering, which raised \$21 million, and conducted another offering in December 1997 that raised \$11 million.

All equity funding is invested in Aastrom's research and development (R&D) efforts and administrative activities required to support that research — the only focus of the company's activities. Thus, as Aastrom succeeded in attracting more private capital, ATP funding constituted a declining proportion of its R&D spending. ATP funds amounted to 23 percent of Aastrom's \$2.6 million R&D budget in 1993 but only 11 percent of its \$4.9 million R&D budget in 1994.

Aastrom does not manufacture products, nor does it intend to. It arranges with third parties to manufacture its candidate products and has agreements with SeaMED and Ethox corporations and Anchor Advanced Products, Mid-State Plastics Division, for the collaborative development and manufacture of certain components of the AastromReplicell™ System.

Large Potential Benefits

Patients — the main beneficiaries of the new technology — are expected to gain from a less evasive procedure that is cost effective, provides greater procedural flexibility, and offers tumor purging benefits. In addition, because of fewer hospital or clinic visits, total costs are expected to be as much as 25 percent less (\$12,000 instead of \$16,000) than costs for PBPC apheresis. Furthermore, if the Aastrom technology substantially decreases the cost of cell transplantation, others who could not have afforded the treatment will now be able to and will benefit. Their benefit may well be life itself, since bone marrow transplantation for cancer patients is frequently a life-saving therapy.

A study of tissue engineering projects, conducted by economists at Research Triangle Institute, Inc. (RTI), under contract to the ATP, noted that Aastrom achieved ATP-project results one to two years earlier than would have been possible without the ATP award.¹ Having the ATP funds also helped the company attract additional equity capital and establish new strategic partnerships. These, in turn, helped accelerate the company's R&D even more.

Wide-scale use of the System is expected to produce large benefits across the economy via reduced treatment costs and lower risks to patients undergoing cell harvesting and transplantation. The RTI study estimates that the present value of expected net benefits from using the System technology for just one type of application — treating cancer patients with solid tumors — exceeds \$100 million.² The study estimates that ATP's contribution of \$1.5 million to the project will generate nearly \$50 million of the expected benefits by speeding the technology's development by one to two years. The RTI study did not attempt to develop estimates based on characteristics of System-based stem cell transplantation that might yield better patient outcomes. It focused only on cost savings.

In addition, the study did not attempt to estimate the value of the effects that a number of other potential applications might have. First use of the System technology is for expanding small amounts of stem cells from bone marrow. It has now been extended to the production of stem cells from umbilical cord blood. Other possible applications include immunotherapy, stem cell gene therapy and cells for solid tissue repair. More benefits can be expected to be generated as the company applies the technology to growing other types of cells — platelets and red blood cells, as well as liver, kidney and nerve tissue — outside the body.

Other possible applications include immunotherapy, stem cell gene therapy and cells for solid tissue repair.



Inserting Cell Cassette into Incubator.

Reducing Viral Contamination in Donated Blood

This ATP project with Aphios Corporation, a small Massachusetts company founded in 1988 as BioEng, developed technology to improve the quality of donated blood in the United States. If the technology is fully developed and widely applied, substantial benefits would accrue to patients. The transfused blood or other therapeutic substances they receive would essentially be free of hepatitis virus, human immunodeficiency virus (HIV, which causes acquired immunodeficiency syndrome, or AIDS) and other viruses that may contaminate vaccines, donated blood, blood-related products, medical instruments and recombinant-DNA proteins.

Solving the Problem of Contaminated Blood

Several sterilization procedures using heat, a chemical, or ultraviolet radiation are already in use, but each method has drawbacks: it may leave unsafe levels of some viruses, be very costly, or damage the blood or plasma. The Aphios sterilization technology, called critical-fluid inactivation (CFI), uses a fluid such as carbon dioxide that is raised above its critical temperature and pressure. Above these levels, the substance cannot be liquefied. In laboratory tests, such fluids exhibit a combination of liquid and gaseous properties, and they have been found to effectively inactivate prototypical

viruses. Critical-fluid viral inactivation uses low temperatures and short process times, so it has a minimal impact on blood and blood-related products. And, at an estimated cost of about \$1 per liter, it is much less expensive than existing technology.

Overcoming Parvovirus

The procedure Aphios developed during the ATP project has been able to achieve 99.9999 percent inactivation or more for most viruses in 20 seconds (99.99 percent inactivation by an individual viral inactivation technique is considered acceptable). The most difficult challenge has been parvovirus.

Parvovirus B19 in blood and blood products has proven difficult to inactivate, not only by the CFI process but by others as well. The virus is relatively benign for patients with healthy immune systems. But it can have serious consequences for those with weakened immune systems, as well as for pregnant women and persons with sickle cell anemia. The current Aphios procedure has achieved 90 percent inactivation of this virus. The company is working on a five-step procedure that is expected to achieve better than 99.99 percent inactivation.

... commercial deployment ... will be much easier if the company can demonstrate that its technology can inactivate parvovirus to an acceptable degree.

... signed a letter of intent with the Northeast Region of the American Red Cross to develop and field-test a viral inactivation prototype ...

The blood industry has established an extremely high standard for new technologies. Therefore, commercial deployment of the Aphios technology will be much easier if the company can demonstrate that its technology can inactivate parvovirus to an acceptable degree. If it succeeds with this task, Aphios will seek to join a larger pharmaceutical company or consortium to further develop and commercialize the process, with substantial investment coming from these sources. In 1998, Aphios sought an arrangement with a consortium of five pharmaceutical companies to complete development of the CFI process.

If a company wishes to commercialize a product for use with donated human blood, it must deal with the American Red Cross (ARC), the source of most blood products used in clinics and hospitals in the United States. Aphios has signed a letter of intent with the Northeast Region of the ARC to develop and field-test a viral inactivation prototype for individual units of blood and is seeking funding for the project.

Health Benefits to Patients and Those Close to Them

If the technology is fully developed and commercialized, benefits are expected to accrue to users of blood and blood-derived products that

PROJECT:

To develop a critical-fluid viral inactivation process to protect the nation's supply of donated blood and blood-related products from contamination by AIDS, hepatitis and other viral diseases.

Duration: 7/1/1992 — 6/30/1995

ATP number: 91-01-0135

FUNDING (IN THOUSANDS):

ATP	\$2,000	67%
Company	1,000	33%
Total	\$3,000	

ACCOMPLISHMENTS:

Aphios developed a procedure using critical fluids to inactivate viruses in blood and established that the process is applicable to a large number of viruses, although to different levels of effectiveness. The following achievements indicate technical progress by the company, which:

- applied for a patent ("Viral Inactivation Method and Apparatus") on technology related to the ATP project;
- presented two papers at conferences on blood-safety issues;
- executed a letter of intent with the Northeast Region of the American Red Cross to develop and field-test a virus inactivation prototype for individual units of blood; and
- submitted a proposal to a consortium of companies to evaluate the viral inactivation technology for use in developing products and processes.

COMMERCIALIZATION STATUS:

Aphios has not commercialized the process yet. The firm has been negotiating with a health care company interested in sponsoring further development and commercialization of the technology. Some early knowledge benefits have emerged from the project via patent disclosures and scientific papers.

OUTLOOK:

Commercialization may occur after more R&D work, primarily on the inactivation of parvovirus. There has been evidence of interest in the technology by the health-care community in general and by the American Red Cross in particular. Benefits are expected to accrue to society if the development of the technology can be completed successfully. However, given the company's financial difficulties, the outlook at this time is uncertain.

COMPANY:

Aphios Corporation (formerly BioEng, Inc.)
3-E Gill St.
Woburn, MA 01801

Contact: Trevor P. Castor

Phone: (781) 932-6933

Number of employees:

3 at project start, 17 at the end of 1997

can be made virus-free with the Aphios technology. Reducing the spread of viral disease is expected to generate large health-cost savings and related benefits to the United States. Users will also benefit if the process based on the new technology is, as expected, less costly than current decontamination procedures. Economic benefits might also extend to people who avoid viral disease because users of blood or blood-derived products decontaminated with the Aphios technology do not become infected and spread the disease.

Without the ATP funds, Aphios officials say, the company would not have conducted the project. Moreover, it would have been impossible for this small company to attract the interest of the health care company or the American Red Cross.

As this report was going to press in late 1998, it was learned that the company had reduced staff and was experiencing financial distress.

Without the ATP funds, Aphios officials say, the company would not have conducted the project.



Molecular Simulations, Inc.
(formerly Biosym Technologies, Inc.)

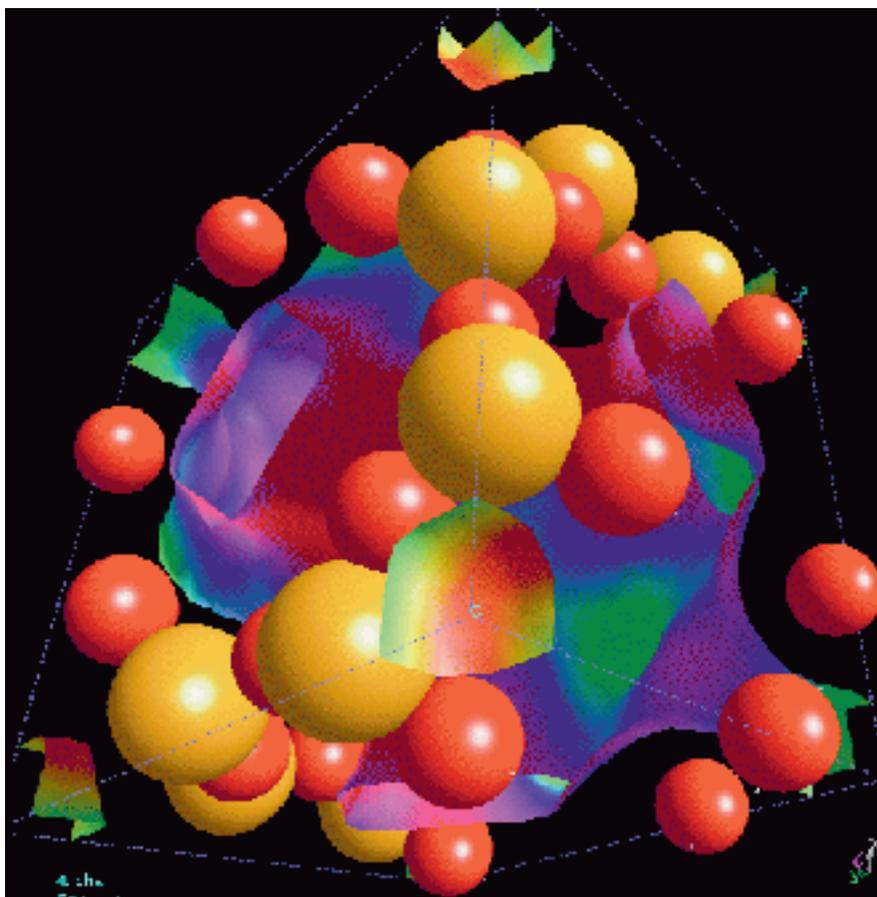
Powerful Software for Designing New Molecules and Therapeutic Drugs

The traditional route to discovering new therapeutic drugs and other useful chemicals should probably be called “semi-automated serendipity.” In the search for new drugs, hundreds of synthetic chemicals and natural substances are put through a long series of trials, starting with effectiveness tests in cell-based assays and concluding with toxicity and effectiveness trials in laboratory animals and, finally, humans. At each stage, the vast majority of substances fail the test and are discarded.

Using Mathematics to Find New Drugs

This ATP project with Molecular Simulations, Inc. (MSI), a small San Diego company that had 170 employees when the project began, combined applied mathematics and computer programming to develop new methods for simulating molecular structures and reactions. The technology is more efficient than conventional molecule-design techniques, a quality

Density functional theory (DFT) proved as accurate as other approaches, yet much less expensive.



The geometrical and electron structure of a siliceous CHA-framework material isotopological with the mineral chabazite. Zeolites and related crystalline microporous solids such as chabazite have industrially useful separative and catalytic properties that are determined by both the micropore architecture and the nature of active sites.

that translates into speedier product development and lower costs.

The ATP-funded effort led to new understanding of density functional theory (DFT), a quantum mechanics method. Most work to understand molecules is mathematical, and DFT is a relatively new form of applied mathematics previously not widely used to simulate molecules. Researchers successfully demonstrated the applicability of DFT to the study of biochemical systems, the backbone of drug

research, showing that DFT is as accurate as other approaches and considerably less expensive.

Applications in New Drugs and Petrochemicals

Prior to its ATP award, MSI was already developing, marketing and supporting a suite of software tools suitable for computing the behavior and properties of molecules. The suite includes tools for bioinformatics, combinatorial library optimization, determination of

PROJECT:

To develop density functional theory (DFT), a type of first principles quantum mechanics, for use in the development of new therapeutic drugs and other substances, an application that is expected to achieve substantial time and cost savings.

Duration: 6/1/1992 — 5/31/1995

ATP number: 91-01-0224

FUNDING (IN THOUSANDS):

ATP	\$1,442	44%
Company	<u>1,867</u>	56%
Total	\$3,309	

ACCOMPLISHMENTS:

MSI successfully demonstrated the applicability of DFT to the study of biochemical systems and developed software that employs DFT to efficiently calculate molecular structures and energies. The software was used to study biochemically relevant systems. It proved as accurate as other approaches, yet much less expensive. Also, the company:

- prepared more than 30 technical papers on the ATP-funded technology for publication in professional journals or presentation at conferences;
- implemented a highly accurate way of applying DFT in the company's Turbomole computer software product;
- expanded its physical plant to accommodate larger R&D and production facilities;
- was a finalist for a *Computerworld* Smithsonian Award, the 1996 Innovator Medal; and
- has grown at a cumulative annual rate of about 20 percent since the end of the ATP project in May 1995.

**Researchers
successfully
demonstrated the
applicability of DFT to
the study of biochemical
systems, the backbone
of drug research . . .**

COMMERCIALIZATION STATUS:

Commercialization is in progress. MSI incorporated the ATP-funded technology into the company's existing Turbomole software package, which has been distributed to more than 100 sites. The ATP-funded technology has also been incorporated into MSI's quantum chemistry workbench software. Benefits from the ATP-funded technology are already accruing to users of MSI software, as well as to users of products developed with the software.

OUTLOOK:

Expectations for this technology and the company are strong. The technology has been incorporated into commercially distributed products that are being used extensively by a relatively small, yet global, community of scientists in academic, industrial and governmental laboratories for rational drug design and petrochemical research. It has potential applications in biotechnology, microelectronics and industrial fine chemicals research.

COMPANY:

Molecular Simulations, Inc.
(MSI; formerly Biosym Technologies, Inc.)
9685 Scranton Road
San Diego, CA 92121

Contact: John M. Newsam

Phone: (619) 546-5391

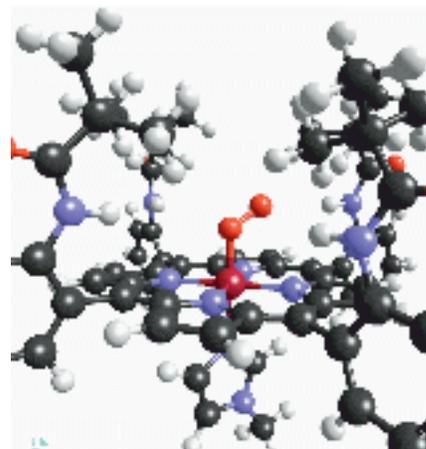
Number of employees:

170 at project start, 292 at the end of 1997

protein structures from amino acid sequences, and structure- and analog-based rational drug design. The ATP project enabled MSI researchers to incorporate the new DFT knowledge into several of these tools. Most MSI software users benefit from access to several different tools and will use more than one of them in a given study.

One of the first MSI tools to be enhanced with the DFT technology was Turbomole, a computer software application that integrates a database of atomic functions, a modern user-interface and mathematical tools like DFT. The computer program calculates tables of molecular characteristics and generates a three-

**. . . prepared more than
30 technical papers . . .
for publication . . .**

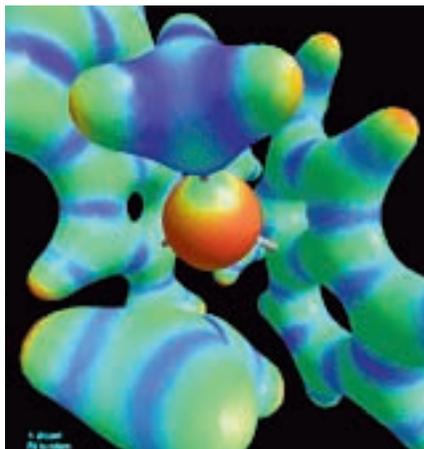


The geometry of a heme complex, optimized by first principles density functional methods implemented in the program DMol, using technology developed under ATP sponsorship. In this molecule, which contains more than 150 atoms, the central iron atom (central, dark red) is coordinated by four nitrogen atoms (blue) of the heme group, and a dioxygen molecule (red).

dimensional structure of the molecule that can be viewed by molecular graphics.

Another tool upgraded with the new technology is DMol, a quantum chemistry program that enables users to make reliable, quantitative predictions about molecular systems. The ATP-funded technology—a DFT-based component of the program—decreases the cost of these types of computation, potentially reducing the cost of designing new molecules. The ATP-funded technology is being used experimentally in petrochemical research, and it has potential applications in biotechnology, rational drug design, microelectronics and industrial fine chemicals research.

**. . . potential
applications in
biotechnology, rational
drug design,
microelectronics and
industrial fine chemicals
research.**



Electron density isosurface of a zirconocene complex, color-coded by electrostatic potential, as computed by the DMol program. The geometrical and electronic structures in metallocene complexes govern the nature of the polyolefin products produced when single site catalysts of this type are used to catalyze olefin polymerization.

Benefits to Companies and Consumers

Because the MSI software is relatively low-cost, enters the discovery and development cycle close to its beginning, and is used by research and development personnel in large organizations, the benefits to the users of the software can be large relative to what MSI earns through software licenses. Such benefits will accrue to chemical, petrochemical, pharmaceutical and biotechnology companies, as well as to companies in other industries that use MSI software incorporating the ATP-funded technology. Benefits will also accrue to people who use therapeutic drugs and other products made by companies using the new technology. In addition, scientists worldwide might benefit from a database of molecular structures developed under the ATP award — MSI is considering making the database available on the Internet.

MSI reports that the ATP funds enabled it to complete research on the DFT technology and incorporate the results into its software products some 18 months earlier than it would otherwise have been able to do. The company, its customers in the pharmaceutical and materials industries, and their customers have all benefited. The project also facilitated the dissemination of new knowledge, particularly via the many scientific papers that were published about the ATP-funded technology.

Company Grows, Announces IPO, is Acquired at a Large Premium

Since the end of the ATP project in May 1995, the company has grown at a cumulative annual rate of about 20 percent. In February, 1997, it filed a Form S1 with the Securities and Exchange Commission, announcing its intention to conduct an Initial Public Offering of stock, and noted that it expected to raise about \$35 million by selling about half of the stock in the company. In February, 1998, the company and Pharmacoepia, Inc., announced that Pharmacoepia would acquire MSI. The acquisition was finalized in June, 1998, in a transaction valued at approximately \$140 million.

. . . scientists worldwide might benefit from a database of molecular structures developed under the ATP award — MSI is considering making the database available on the Internet.

Thermo Trilogy Corporation
(original awardee: AgriDyne Technologies, Inc.)

Bioengineering of a Safe, Organic/Chemical Insecticide

Every year millions of tons of chemical pesticides are sprayed or irrigated onto plants in fields and gardens throughout the United States. Protected from weeds and insects, these plants flourish and grow to provide food and visual delight for us all. Chemicals used for pest control, however, sometime turn out to be poisonous for humans, and the results are often tragic. Consequently, efforts are under way to reduce the need for toxic chemical pesticides and, in the process, to eliminate the adverse side effects they can bring.

Reducing the Risk of Toxic Pesticides

One promising approach to reducing the hazards of pesticides is to use genetically engineered organic compounds based on naturally occurring pesticides that are harmless to humans. The ATP project with AgriDyne Technologies offered a novel way to do this by taking advantage of large-scale biochemical production. AgriDyne, founded in Utah in the early 1980s as Native Plants, was a small company that would have been unable to pursue this research without the ATP award.

Scientific knowledge generated by the ATP project . . . is disclosed in two patents and may be important to the genetic engineering of other plant extracts.

A Nontoxic, Chrysanthemum-Based Pesticide

The technology AgriDyne developed during its ATP project is based on the chemistry of pyrethrins, a group of six closely related natural insecticides derived from pyrethrum, a type of chrysanthemum. Pyrethrins kill insects on contact, have low toxicity for mammals, degrade shortly after application and produce no harmful residues. The only current source for natural pyrethrins is chrysanthemum from east Africa. But, according to AgriDyne's proposal to ATP, supplies were neither stable nor sufficient to meet the worldwide demand.

Although pyrethrins can be synthesized in the laboratory, production via traditional chemical processes is difficult and expensive. AgriDyne's alternative was to genetically engineer yeast cells to produce chrysanthemyl alcohol, a precursor that is then chemically converted to chrysanthemic acid. This, in turn, can be used to produce commercial quantities of pyrethrin.

Business Upheavals Stall Technology

AgriDyne achieved most of the technical goals of the project, but production costs were higher than predicted. The company encountered financial problems that forced it to close in 1995, just as the project was ending. AgriDyne apparently did not have enough management resources to handle the challenges of both developing the technology and commercializing a product. The firm was acquired by Biosys of Columbia, Md., another biopesticides company, which decided not to make the investment required to commercialize the ATP-funded AgriDyne technology.

Biosys, in turn, declared bankruptcy in 1996. Its assets, including patents, were acquired by Thermo Trilogy, the second largest biopesticides company in the world. Thermo Trilogy officials reported having no current plans to commercialize the ATP-funded technology, since the cost today of procuring chrysanthemyl from Africa is lower than the expected cost of producing pyrethrin with the new technology. In addition, they say, detailed knowledge of the scale-up process for the technology (requirements for physical plant invest-

The company encountered financial problems that forced it to close in 1995, just as the project was ending.

PROJECT:

To develop a genetic engineering process for producing pyrethrin, a natural insecticide from chrysanthemums that is nontoxic to mammals but was available only from Africa in limited, unstable supplies. The technology would provide a less-costly, stable domestic source of supply.

Duration: 6/1/1992 — 5/31/1995

ATP number: 91-01-0071

FUNDING (IN THOUSANDS):

ATP	\$1,200	37%
Company	<u>2,012</u>	63%
Total	\$3,212	

ACCOMPLISHMENTS:

AgriDyne achieved most of its technical goals and received two project-related patents:

“Storage Stable Pesticide Compositions Comprising Azadirachtin and Epoxide”

(No. 5,352,697: filed 7/28/1992, granted 10/4/1994) and

“Chrysanthemyl Diphosphate Synthase, Corresponding Genes and Use in Pyrethrin Synthesis”

(No. 5,443,978: filed 6/25/1993, granted 8/22/1995).

COMMERCIALIZATION STATUS:

No commercial product has yet been produced.

OUTLOOK:

Commercialization is uncertain, owing to the dissolution of AgriDyne, current market conditions that make the new production approach too costly to compete with natural sources of supply, and lack of plans, at this writing, by Thermo Technology (which now owns the intellectual property) to pursue further development. Scientific knowledge generated by the ATP project, however, is disclosed in two patents and may be important to the genetic engineering of other plant extracts. The knowledge has potential applications in pharmaceuticals and specialized materials and chemicals, as well as in pesticides.

COMPANY:

AgriDyne Technologies, Inc.
(acquired by Biosys, Inc. in 1995; Biosys assets acquired by Thermo Trilogy in 1996)
Thermo Trilogy Corporation
7500 Grace Drive
Columbia, MD 21044

Contact: Ramon Georgis

Phone: (410) 531-4711

ment, as well as information on the predictability of a viable, consistent production yield) was unknown to them and their counterparts at Biosys, and they found it difficult to assess AgriDyne’s ATP project. Both companies considered further pursuit of the technology too risky for them.

Although no commercial product has yet resulted from the ATP-funded technology, new bioengineering knowledge has.

Gains in Bioengineering Knowledge

Although no commercial product has yet resulted from the ATP-funded technology, new bioengineering knowledge has. Some of it has been disclosed through two patents. But AgriDyne’s manufacturing know-how was apparently not passed on to the company’s successors. Should events in Africa decrease the supply or increase the cost of natural pyrethrin, the AgriDyne approach may be resurrected by funding development of the needed manufacturing skills.

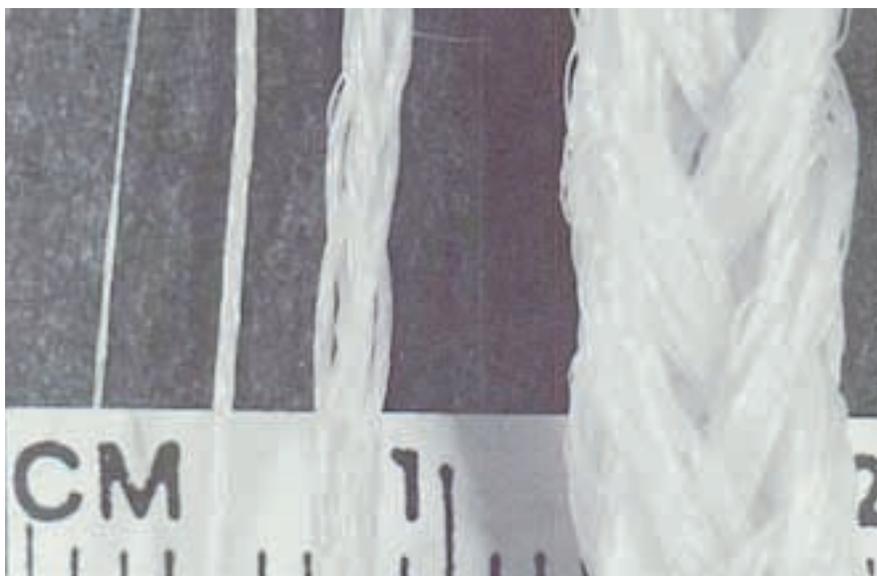
Tissue Engineering, Inc. (TE)

Prostheses Made of Biomaterials That Regenerate Body Parts

From its beginning, the field of bioengineering has focused on providing the best artificial devices — hearing aids, artificial limbs and other prostheses — to replace body parts that are missing, broken or dysfunctional. This ATP project with Tissue Engineering (TE), a biotechnology start-up company, takes bioengineering far beyond artificial replacements to a technology that regenerates, rather than replaces, lost or damaged tissues. Although this claim sounds like science fiction, it is in fact quite real. And it promises to produce real medical benefits in the very near future.

Technology to Regenerate Lost or Damaged Body Parts

TE is pioneering a new class of biomaterials called ADMAT (animal-derived extracellular matrix). The idea behind the company's ATP project is to use ADMAT materials in collagen-scaffold "prostheses" to replace damaged or dysfunctional tissues and organs. The prostheses are designed to provide templates that mobilize the body's own cells and induce them to rebuild the lost tissue, gradually replacing the prosthesis itself. Regeneration of body parts requires a biomaterial with a structure, components and chemical signals that allow the body's tissue cells to recognize, respond to and remodel the material without rejecting it as foreign.



Collagen fiber and braided structures from collagen fiber: (a) single collagen fiber, (b) 8-ply collagen fiber braid, (c) 64-ply collagen fiber braid, (d) 512-ply collagen fiber braid.

Demand for ADMAT Materials

ADMAT materials are derived from the by-products of land and marine animals processed for food. The material can be spun into fibers and woven into fabrics using techniques borrowed from the textile industry, or it can be formed into foams, sheets and films. ADMAT can be used to enhance collagen scaffolds for vascular

grafts, ligaments, tendons, periodontal tissue and similar reconstructions.

During the ATP project, TE successfully developed techniques and procedures for extracting and storing a mixture of collagens and for preserving the desired characteristics of the extracellular matrix. The company developed new materials for hosting the matrix and a process for adding the matrix to collagen fibers in the course of spinning.

The demand for products the company plans to offer clearly exists. The lag time, however, between technology conception and market availability — particularly for medical treatments — is long. Tissue-engineered products face clinical trials and other regulatory hurdles, in addition to technical and market-introduction barriers. The company is making good progress in navigating these barriers in accord with its technical and business plans.

This ATP project . . . takes bioengineering far beyond artificial replacements to a technology that regenerates, rather than replaces, lost or damaged tissues.

atp



Collagen fiber decorated with ADMAT microparticulates via ATP-funded patented process.

Commercialization is in progress. TE has placed periodontal prosthesis prototypes with potential customers for testing. It has created other products for research, testing and diagnostic applications. These activities are not regulated, so commercialization can happen more speedily. In addition, it has formed a venture with Wright Medical Technology for commercialization of orthopedic applications. TE is also in discussions with several other companies to commercialize other applications, such as a line of skin and wound-healing products.

TE has placed periodontal prosthesis prototypes with potential customers for testing.

Large Potential Benefits for Society

The eventual successful commercial introduction of the ATP-funded technologies will bring large health gains to patients with many forms of medical problems, ranging from dental to cardiovascular. Procedures and materials that would enable the regrowth of ligaments and cartilage in knees and enable dental tissue to regenerate with a single surgery — at costs lower than those offered by alternative medical approaches today, and that one day may even facilitate organ regeneration — would have great benefits for society.

These potential benefits are likely to be huge because of the large number of patients who could use these prostheses, the advantages the TE approach has over currently available alternatives, and improvements in the ability of patients to function as a result of using the new technology. The ATP award is playing an

PROJECT:

To develop techniques and procedures for processing tissue, extracting and storing collagen, and spinning and weaving collagen fibers into fabrics and other forms suitable for human prostheses that could induce the body's own cells to rebuild lost tissue while gradually replacing the prosthesis.

Duration: 3/1/1993 — 2/28/1996

ATP number: 92-01-0133

FUNDING (IN THOUSANDS):

ATP	\$1,999	48%
Company	<u>2,128</u>	52%
Total	\$4,127	

ACCOMPLISHMENTS:

TE accomplished its technical goals. The company developed procedures for processing a tissue-specific extracellular matrix rich in cytokines (cell-generated proteins), extracting and storing type I collagen (a material present in all tissues), and spinning collagen into fibers that can be woven into prosthetic fabrics. The company:

- received two patents for technologies related to the ATP project:

“Apparatus and Method for Spinning and Processing Collagen Fiber”

(No. 5,562,946: filed 11/2/1994, granted 10/8/1996) and

“Bipolymer Foams Having Extracellular Matrix Particulates”

(No. 5,709,934: filed 11/22/1994, granted 1/20/1998);

- applied for three other patents related to the technology;
- made several presentations at conferences and workshops; and
- formed a joint venture with Wright Medical Technology, Arlington, Tenn., to develop and distribute products based on the ATP-funded technology for applications involving ligaments, tendons, cartilage and other musculoskeletal parts.

COMMERCIALIZATION STATUS:

A commercialization venture has been formed for orthopedic applications. Prototypes are in testing, although no product has yet entered the market. Patent disclosures and a joint venture to commercialize the technology may be providing useful knowledge to other researchers in the field.

OUTLOOK:

This project is on track for market entry in the very near future. The technology is scheduled to be used first in the fabrication of periodontal prostheses and orthopedic applications. Ideas for skin and wound-healing products are also being explored by the company with potential customers.

COMPANY:

Tissue Engineering, Inc. (TE)
451 D St., Suite 807
Boston, MA 02210

Contact: Eugene Bell

Phone: (617) 946-0520

Number of employees:

1 at project start, 18 at the end of 1997

important role in bringing these benefits to society, because applications of the new technology are about two years ahead of where they would have been without ATP funding.

A recent detailed case study by the Research Triangle Institute estimated that TE's ADMAT technology could be expected to generate about \$33 billion (in present value dollars) in net benefits for society in a single medical application area: anterior cruciate ligament repair.³

The study estimated that about 100,000 patients per year with ligament damage would be eligible for the new treatment, that the number using the Tissue Engineering technology would start at 9,000 in the first year of availability and grow to 72,000 ten years later, supplanting an increasing percentage of alternative technologies currently in use. The study

incorporated estimated benefits from quality-of-life improvements, using a “quality-adjusted-life-years” index value. It estimated that about \$15 billion of the expected benefits would be attributable to ATP's accelerating the technology development by two years.

... formed a venture with Wright Medical Technology for commercialization of orthopedic applications.