A SHORT VISIT WITH MARROW TE...

ATS: DEVICES AND DESIRES

SAN DIEGO, Calif.—It was five or six years ago that Arthur Benvenuto first started talking about his company. It was called Marrow-Tech, a kitchen-table kind of an operation based in one of New York's outer boroughs. Marrow-Tech was planning to grow replacement bone marrow for transplantation. At the company's heart was a method for laying down stromal cells and collagen I and III on a textile matrix, forming a base on which cells could grow in a normal, tissue-like orientation. Competitors in the blood-and-blood-substitute market dismissed Marrow-Tech as low-tech. They said things like, "there's nothing really new in what they're doing" and "it's technique, not technology."

Today, the company is called Advanced Tissue Sciences (ATS). It announced a name change just before Christmas; on the following day, ATS announced a 2-million share secondary public offering (it was listed in June), which will add to the $15-$18 million it already has in the bank. It is lodged comfortably in a 22,000-square-foot, one-story, good-manufacturing-practice (GMP), research-and-manufacturing building on the bluff overlooking the Pacific in La Jolla, CA. ATS's primary business is now in culture-grown natural human skin (derived from neonate foreskins) for transplantation and toxicology testing: Last year, it started marketing Skin^2, a toxicology testing kit based on a 24-well format. And this year, it expects to garner U.S. Food and Drug Administration (FDA, Bethesda, MD) marketing approval for DermaGraft, a histocompatible human skin for transplant treatment. The first approvals will probably come for the treatment of burns, with treatment of venous and decubitus ulcers to follow.

Yet the core technology remains the same. And so does the chief executive officer.

How did an East Coast service business become a West Coast device-manufacturing business?

The company has made a number of choices unusual in medical biotechnology. First, Benvenuto and Gail Naughton, the company's director of research and chief operating officer, have studiously avoided the drug and biologic markets, focusing exclusively on devices, which have lower developmental costs and shorter research-and-development and clinical-approval cycles. And second, the company is marketing-driven. Both of ATS's products have been developed in close cooperation with consumers, with a two-fold imperative: get the users to define and design the product they want most; and get opinion leaders "signed on" and enthusiastic from the outset.

These efforts are directed, Benvenuto says, at providing customers with attractive, cost-effective alternatives to products in existing high-profile, high-value markets.

In keeping with its market mandate, the company has reduced its sales pitch for each product to a very short list of points that must be hit—hard and over and over—on each sales contact. A salesman pushing Skin^2, for example, will unfailingly note that the product is totally human, yields high *in vitro* correlation with *in vivo* tests, is reproducible, and is completely mechanistic (as opposed to subjective).

DermaGraft, on the other hand, is sold as the universal, transportable dermal replacement.

Toxicology testing

ATS worked closely with toxicologists at Battelle Memorial Institute to develop Skin^2. Often in daily contact, Naughton says. The object was, first, to assure the high correlation with the conventional animal tests that have drawn activist fire and consumer ire. Second, they aimed to put together a package the testers would find convenient.

The result is a self-contained, custom 24-well plate (allowing testing of two compounds in five dilutions with a known positive) with a two-week shipping life and a two-week shelf life. The package intentionally allows researchers to collect and analyze toxicant byproducts—the products of cell metabolism and cell death alike—which can tell more about toxicant mechanisms than conventional toxicology tests, ATS officers say.

For the U.S. toxicology market, the company now maintains a three-person direct-sales operation. The company also has agreements with two Asian distributors, including Oriental Yeast (Tokyo), and recently announced a European distribution agreement with Janssen Biotech in Belgium.

When *Bio/Technology* dropped in last fall, Benvenuto and company were deeply encouraged by the European Community's newly adopted specifications for animal-test substitutes: the new continental standards specify products based on human skin produced in GMP facilities.

Skin grafts

ATS product developers also devoted a lot of time to learning how to package and ship their skin-graft product. That process led them into the garment business (to learn about the manufacturing characteristics of the polyglycolic acid and other textile meshes on which the cells are grown) and into the arcana of plastics (where they needed to master the machining of Teflon, a notoriously hard-to-fabricate material that ATS welds into the manila-envelope-size pouches in which the tissue is aseptically grown and shipped). Over a two-month period, the polyglycolic acid mesh hydrolyzes physiologically (as opposed to enzymatically, which can raise problems of antigenicity, Naughton says).

DermaGraft will aim initially at the burn-treatment market, which ATS estimates could be worth $400 million to $1.5 billion a year in the U.S.: some 25,000-50,000 patients require an average of about three square feet of replacement tissue apiece, and ATS expects to price the product at $5,000-$10,000 a square foot. ATS will not have this market to itself; Marion Merrell Dow (Kansas City, MO) already offers a competing product, Integra.

The ulcer markets are much larger, Naughton and Benvenuto say. The patient population numbers in the millions, and conventional-treatment costs average $25,000.

For grafting applications, ATS offers two different products: a full thickness product (consisting of epidermis and dermis together) and layers of the dermis alone (to be used in combination with an autograft of the patient's own top skin).

In general, Naughton points out, surgeons must now perform two separate operations to complete a skin graft: one to lay down the dermis and basement tissues, and another after these have established themselves to lay down a mesh of epidermis which then spreads to skin over the wound. With DermaGraft, Naughton claims, the surgeon can put down autograft mesh directly over single-thickness DermaGraft during a single operation. The matrix seems to offer a much firmer bed and the skin grows in better than in the customary two-step procedure, reducing the problem of epidermal sloughing.

Down the road

Down the road, Benvenuto says, ATS is working on extending its base technology (well defended by patents) into model and replacement-tissue devices drawn from other organ systems, among them the pancreas, liver, and oral mucosa (models for studying periodonal disease and possibly for dental implants). The company is also working on various cartilaginous tissues that create natural collagen for prosthetics (for lining artificial joints), natural joint resurfacing (to repair the ravages of arthritis, trauma, and temporal mandibular joint disease), repairing slipped or degenerated vertebral disks, and plastic surgery (as a natural structural material).

—Douglas McCormick