State of the Cure

As the State of the Cure document nears completion, a decade of progress emerges.

You are here. It’s a phrase commonly seen on maps in airports or shopping malls to help orient the reader and put things into perspective. It’s also a good way to sum up what the State of the Cure document will mean to the Alpha-1 Foundation, our supporters, and Alphas everywhere.

This summer, the finalized State of the Cure will be presented at the Alpha-1 Association 2008 Annual Education Conference by Adam Wannen, MD, Scientific Director of the Foundation.

One way to determine where we are is to look at some numbers. From 1996 to 2006, the National Institutes of Health supported 125 research grants to 93 principal investigators in the United States. The cost was $33 million. Over the same time frame, the Foundation provided support for 90 investigators in six countries. We invested nearly $28 million to support Alpha-1 research and programs in 50 institutions in North America and Europe. Included in this $28 million investment was more than $9 million (32%) spent on competitive grant awards, the primary source of scientific discoveries.

The nature of cutting-edge Alpha-1 studies and the long-term nature of many of the studies, combined with severe government funding cutbacks, will require ever-increasing sources of private funding in the near future. The State of the Cure will provide clear, detailed explanations of the current state of research and development, in easy-to-understand language. It will define where we are and where we can go. It will be a high-resolution snapshot of how funding has been spent, and will indicate where funding will be most needed in the future.

To determine where we are with respect to a cure, it is necessary to define what we mean by a cure. In essence, we are simultaneously looking for ways to prevent, halt and reverse the disease, and to prevent inheritance of Alpha-1.

For instance, in this issue of Alpha-1-To-One, you’ll read about the latest advances in gene therapy research [see page 14]. You’ll learn about the current state of inhaled augmentation therapy and how it may develop into a therapeutic solution in the near future [see page 12]. And you’ll discover how a major effort to standardize CT scanning to look at COPD and Alpha-1 progression will make research into new therapies faster, cheaper and more reliable [see page 3].

“The State of the Cure will demonstrate the progress we’ve made in the past 10 years,” says Foundation President and CEO John Walsh. “It will underline the importance of responding to the numerous therapeutic pathways identified, and of making certain we have the resources to support efforts to test and commercialize new products and therapies for liver- and lung-related Alpha-1.”

In many ways, the State of the Cure reflects the state of commitment of Alphas to find ways to help the Alpha-1 community. Every story you read in this issue relates to that commitment. Researchers, doctors, patients, legislators — examples of people doing what they can do to make a cure a reality. You are here. And that’s right where we need you.

For information about organizing a fundraising event to benefit Alpha-1 research, contact Angela McBride at 1.888.825.7421, ext. 233, or amcbride@alphaone.org.
Putting Research on Fast-forward

CT scanning is set to revolutionize the way COPD research is done.

Sometimes you need to define progress before you can make progress. That was the basic premise behind a recent workshop on CT scanning.

The conference — the 10th in the Gordon L. Snider Critical Issues Workshop Series — was hosted by the Alpha-1 Foundation and COPD Foundation in Washington, DC, in April.

Experts in CT scanning from the US, Canada, Europe and Japan met to determine how best to standardize the technology to measure the progression of COPD. Harvey Coxson, PhD, was chair.

"In the past, researchers used pulmonary function tests such as spirometry to measure the severity of COPD and the effectiveness of treatment. Those tests could detect changes in lung function but not in the lung’s structure,” said Adam Wanner, MD, the Alpha-1 Foundation’s Scientific Director. "CT scanning is the best method to assess structural changes by non-invasive methods."

While CT scanning shows much promise, “The procedure has not yet been fully standardized, and no consensus has yet been reached on the best way to quantify many of the characteristics of COPD,” Wanner said. “That was one of the reasons that the CT scanning workshop was convened.”

According to Foundation President and CEO John Walsh, “The workshop provided a critical forum to substantiate the validity of using CT imaging for early detection, for tracking disease progression and for use as a clinical trial endpoint.”

Walsh said CT imaging “will be more accurate, will decrease the number of study subjects required and decrease the length of time for clinical trials. It’s essential that we standardize this method of testing so we can accelerate the development of new therapies.”

“We hope to publish the conference proceedings in a journal of the American Thoracic Society,” said Wanner. “The need to proceed with this line of investigation is very strong. In the future, CT scanning will be an important way of looking at COPD, its progression and the efficacy of treatment.”

The workshop was sponsored by AlphaNet, Arriva Pharmaceuticals, Baxter Healthcare, CSL Behring, Kamada, Roche Pharmaceuticals, Spiration, and Talecris Biotherapeutics.
I remember that it was a pretty interesting week for me. It was in 1991. I was writing and editing a national sports newspaper at the time — The National. One Friday, the boss came to me and said that he was sorry, but that we were going out of business. I had the weekend to mull that over. Then on Monday, my doctor called and told me I had Alpha-1. The newspaper had been on the ropes for a while, but this was a real one-two punch.

I was a little over 40 when I started noticing shortness of breath. The first place I noticed it was on the tennis court. I had smoked a little and originally thought it had something to do with that. After a while, I thought I really ought to see a specialist. By ironic coincidence, I had a daughter, Alex, who died of cystic fibrosis at a very young age. So, I knew whom to turn to. I called a CF specialist and was tested. They found that my lung capacity had indeed fallen a little, but it was nothing to get excited about. Everyone just assumed I had some sort of allergy. Of course, they never could find one.

After about 11 years of this, I knew I had been declining. Not in a dramatic way, but I couldn’t ignore it. All that time I’d get checked out, but no one ever came to a conclusion about what was wrong with me. Then I went to see a bright young doctor who immediately suspected I had Alpha-1. He tested me, and on that Monday in 1991, it was confirmed.

I’d never heard of Alpha-1. So, it was almost a relief that I knew there was a name for what I had. My doctor was very candid right away and told me it was a fatal, incurable disease. Fortunately, he told me right then of a new drug called Prolastin. I went to see another specialist, Dr. Edward Eden, in New York, and he described the disease in detail and agreed that Prolastin might help me.

Now, nobody likes to hear they have a fatal disease, but it didn’t disable me emotionally. Intellectually, I figured I’d be in bad shape in about five years. I was 52 at the time. Of course, I’d seen someone I loved die of a lung disease. I knew how horrible that was. I knew what faced me. But I was relatively healthy at the time. I guess it was easier for me to not think too much about the future right then.

I’m 69 years old now, and while I can’t do anything strenuous and am taking lots of medication, I really can’t complain. Yes, my lung function has declined somewhat over the years. But I’m still doing pretty much the same things I was doing when I was diagnosed.

There’s such a range with this disease. The same is true of CF. Why am I relatively active at my age while other people have to get lung transplants at age 30? My daughter died at the age of 8, and there are other CF patients who don’t get serious symptoms until they are in their 30s.

This past winter, I did a piece that aired on HBO’s Real Sports with Bryant Gumbel. I met and interviewed Len Geiger, a young man with Alpha-1 who, despite having had a lung transplant, continues to push the boundaries, run marathons and act as an inspiration to all of us. We also met with the family of the young woman whose tragic death meant life for Geiger — he was the recipient of the lungs she donated. It was an emotional story. And when it ran, I made the decision to mention on air that I, too, had Alpha-1. I normally don’t inject my own personal.
Frank Deford with daughter Scarlet, son Christian and wife Carol

life into my stories. But I told Bryant that if I do this story and don’t mention my Alpha-1, people who know I have it will think I’m embarrassed. But when I see someone like Len Geiger and think of the people who die from this disease, I realize how lucky I am.

In my own case, I imagine I stretch the limits of the disease. John Walsh tells me he is amazed at how often I fly. And I do it without oxygen. When I stand up on a plane to go to the bathroom, I do it very, very slowly and walk almost in slow motion. You take the limits as far as you can and don’t do the things you can’t do. I might be walking with someone who is moving at a normal pace and they can’t understand why a 6’4” guy is lagging behind. Or when I have to fly on one of those stupid little planes, the kind with no Jetway; by the time I lug my bag up a flight of those stairs, I’m really gasping and struggling. People want to call a doctor. It’s a bit embarrassing. But of course, in the full scheme of things, that’s pretty small potatoes.

These days, I exercise with oxygen. I have a treadmill and a stationary bike, and I lift weights. Exercise is very helpful for people with this disease, both physically and emotionally. I think it’s important to stay in a good frame of mind. That’s not always easy to do, of course. Sometimes, when I have a couple of bad days in a row, I think, “Okay. This is it. The beginning of the end.” It’s hard to stay “up” at times like that. It’s easy to say “Hey! Let’s face another day!” But when things are going badly, it’s difficult to do. But I’ve always come out of those valleys.

One of the things I keep in the back of my mind is the way Alex conducted herself. The fact that she was so extraordinarily brave at such a young age — well, I’d be insulting her memory if I wasn’t up to her standards when I’m tested in that way. I’ll be ashamed of myself if I don’t live up to her example.
Two for the Road

Hap and Diane Eaton ride cross-country for her brother-in-law, Dugan — and for Alpha-1 awareness.

Hap and Diane Eaton enjoy each other’s company. A necessity, when you spend a full year in the daily close proximity of a two-seater bicycle. It helps that the Eatons see themselves as a team, sharing in the joy of making a difference. In May of 2007, Hap and Diane set out to ride 10,000 miles around the United States on a tandem bike. It was a long-time goal, and an eye-grabbing way to raise awareness about Alpha-1.

The best part about the trip: “The people.” Whether it was the drivers who slowed down for them (the most considerate, believe it or not, in Los Angeles), a cyclist who invited them in for Christmas dinner with his family, or Karen Erickson, who biked for nearly 70 miles alongside them, there have been plenty of memorable moments. “We don’t believe in miracles, we depend on them,” says Hap.

But the Eatons are also well prepared. Hap takes care of all of the bike maintenance. The bike — which is over 20 years old — gets an annual rebuilding, so they’ve had only a few minor mechanical problems. The tandem weighs 180 pounds, and pulls a cargo trailer carrying 18 more. The Eatons are packing light: Each only has three sets of cycling clothes for the entire 10,000 miles. (They’re usually able to find a laundromat in each town they visit.)

Diane’s role is maintaining their daily nutrition. Though they camp as much as possible, they’re still able to get a good meal. Their titanium cooking gear includes a mini stove, two pots and a skillet. It helps that they’re pretty easygoing about food: they can boil water, cook up a can of soup or baked beans, and as long as there’s a “Take 5” candy bar within reach, they’re all set.

Breakfast is a meal they take seriously: Diane gets their daily energy going with oatmeal, bananas, peanut butter, bagels, or yogurt.

They also have more than food giving them energy: Back home in Ohio they have Diane’s brother-in-law Dugan, who gives them another reason to keep going.

Dugan Reed, 49, was diagnosed with Alpha-1 about 20 years ago. Seven years ago, he went to the Cleveland Clinic for a lung transplant evaluation. The transplant team told him he would need to lose 70 pounds before he could get on their waiting list. That’s when he began to ride a bike regularly.

With the help of AlphaNet Coordinator Mary Pierce and his sister-in-law Diane, Dugan began training to get back into shape. Over the next nine months, he lost the excess weight and got strong enough to participate in the Ohio Bike Adventure, a 350-mile course, wearing his oxygen. (Dugan, formerly a welder, built a three-tank oxygen rack on the back of his bike.)

Dugan is still waiting to be approved for the transplant list. His weight is acceptable but the doctors say he isn’t “sick enough”. Unfortunately, he’s too sick to be as active as he’d like. He can’t handle long-distance bike rides anymore. His last bike trek was around Mother’s Day of 2007, “and it really trashed me,” he says.

The Eatons see their long ride as just a way of giving back to the Alpha-1 community. “You (the Alpha-1 Foundation, AlphaNet, and the Alpha-1 Association) have really made a big impact on many people’s lives,” Diane says. “The last 20 years have been a journey.”

They bring a piece of Dugan with them on every ride: a red bandana that he always wore when he rode. They have pictures with the bandana everywhere, regularly uploaded onto their internet blog with their trusty super-light laptop. (“It’s waterproof, crash-proof and Eaton-proof,” Diane says.)

The trip hasn’t been easy. The temperature hit 115 degrees as they rode through Montana last August; down to 25 in Texas this winter. Hap’s mother died in January, so they had to fly home to her funeral. Diane got a painful case of shingles. Then there’s all that enforced closeness; after the trip is over, Diane says, “I’m going to write a book on relationships.”

But overall, “It’s been surprisingly wonderful,” said Hap. “People will just ignore you if you show up in a car. But drive up on a big yellow tandem bike and people will go out of their way to talk to you.”

Hap and Diane Eaton enjoy each other's company. A necessity, when you spend a full year in the daily close proximity of a two-seater bicycle. It helps that the Eatons see themselves as a team, sharing in the joy of making a difference. In May of 2007, Hap and Diane set out to ride 10,000 miles around the United States on a tandem bike. It was a long-time goal, and an eye-grabbing way to raise awareness about Alpha-1.

The best part about the trip: “The people.” Whether it was the drivers who slowed down for them (the most considerate, believe it or not, in Los Angeles), a cyclist who invited them in for Christmas dinner with his family, or Karen Erickson, who biked for nearly 70 miles alongside them, there have been plenty of memorable moments. “We don’t believe in miracles, we depend on them,” says Hap.

But the Eatons are also well prepared. Hap takes care of all of the bike maintenance. The bike — which is over 20 years old — gets an annual rebuilding, so they’ve had only a few minor mechanical problems. The tandem weighs 180 pounds, and pulls a cargo trailer carrying 18 more. The Eatons are packing light: Each only has three sets of cycling clothes for the entire 10,000 miles. (They’re usually able to find a laundromat in each town they visit.)

Diane’s role is maintaining their daily nutrition. Though they camp as much as possible, they’re still able to get a good meal. Their titanium cooking gear includes a mini stove, two pots and a skillet. It helps that they’re pretty easygoing about food: they can boil water, cook up a can of soup or baked beans, and as long as there’s a “Take 5” candy bar within reach, they’re all set.

Breakfast is a meal they take seriously: Diane gets their daily energy going with oatmeal, bananas, peanut butter, bagels, or yogurt.

They also have more than food giving them energy: Back home in Ohio they have Diane’s brother-in-law Dugan, who gives them another reason to keep going.

Dugan Reed, 49, was diagnosed with Alpha-1 about 20 years ago. Seven years ago, he went to the Cleveland Clinic for a lung transplant evaluation. The transplant team told him he would need to lose 70 pounds before he could get on their waiting list. That’s when he began to ride a bike regularly.

With the help of AlphaNet Coordinator Mary Pierce and his sister-in-law Diane, Dugan began training to get back into shape. Over the next nine months, he lost the excess weight and got strong enough to participate in the Ohio Bike Adventure, a 350-mile course, wearing his oxygen. (Dugan, formerly a welder, built a three-tank oxygen rack on the back of his bike.)

Dugan is still waiting to be approved for the transplant list. His weight is acceptable but the doctors say he isn’t “sick enough”. Unfortunately, he’s too sick to be as active as he’d like. He can’t handle long-distance bike rides anymore. His last bike trek was around Mother’s Day of 2007, “and it really trashed me,” he says.

The Eatons see their long ride as just a way of giving back to the Alpha-1 community. “You (the Alpha-1 Foundation, AlphaNet, and the Alpha-1 Association) have really made a big impact on many people’s lives,” Diane says. “The last 20 years have been a journey.”

They bring a piece of Dugan with them on every ride: a red bandana that he always wore when he rode. They have pictures with the bandana everywhere, regularly uploaded onto their internet blog with their trusty super-light laptop. (“It’s waterproof, crash-proof and Eaton-proof,” Diane says.)

The trip hasn’t been easy. The temperature hit 115 degrees as they rode through Montana last August; down to 25 in Texas this winter. Hap’s mother died in January, so they had to fly home to her funeral. Diane got a painful case of shingles. Then there’s all that enforced closeness; after the trip is over, Diane says, “I’m going to write a book on relationships.”

But overall, “It’s been surprisingly wonderful,” said Hap. “People will just ignore you if you show up in a car. But drive up on a big yellow tandem bike and people will go out of their way to talk to you.”

Hap and Diane Eaton ride cross-country for her brother-in-law, Dugan — and for Alpha-1 awareness.
The Alpha-1 Foundation, AlphaNet and the Alpha-1 Association have really made a big impact on many people’s lives. The last 20 years have been a journey.

If you’re interested in marking your own trail, the Eatons suggest you check out the Adventure Cycling Association, which provides maps, efficient biking routes and safety information.

You can find the ACA website at adventurecycling.org.

Or become part of the journey and read the Eatons’ blog at www.outbikin.blogspot.com. You can also make a donation at their Alpha-1 Foundation fundraising site, located at www.firstgiving.com/eatons.
Researchers have begun using tissue and DNA from the Alpha-1 Foundation DNA and Tissue Bank at the University of Florida. The results are fascinating, some of them being reported for the first time. Here are three researchers whose work has included Tissue Bank material; their stories follow.

Farshid N. Rouhani, MS, Senior Scientist and Assistant Director, Alpha-1 Research Program, University of Florida College of Medicine, studied the effect of augmentation therapy on chronic inflammation in ZZ Alphas.

Farshid Rouhani’s study was to evaluate chronic inflammation, a common problem observed among Alphas.

He measured the levels of C-reactive protein (CRP), a marker of systemic inflammation, in the blood plasma of more than 500 ZZ Alphas enrolled in the Alpha-1 Foundation DNA and Tissue Bank.

“We hypothesized that IV augmentation reduces systemic inflammation determined by CRP levels in individuals with Alpha-1 Antitrypsin Deficiency,” Rouhani says.

Rouhani demonstrated that CRP levels, on average, are higher than normal in Alphas. In addition, there was a negative correlation between CRP levels and FEV1 (a measure of lung function). In other words, lower lung function is associated with higher systemic inflammation.

In fact, Alphas with significant lung function impairments who are on IV augmentation have 2.5 times lower levels of CRP compared to Alphas not on therapy.

“This preliminary data shows that IV augmentation reduces systemic inflammation in alpha-1 antitrypsin deficient individuals with significant lung function impairment,” he said.

Rouhani presented these findings at the American Thoracic Society (ATS) 2007 International Conference and is working on a manuscript for publication.

Richard N. Sifers, PhD, Associate Professor of Pathology (with joint appointments in the department of Molecular and Cellular Biology, and Molecular Physiology and Biophysics) at Baylor College of Medicine in Houston, TX is examining how the liver disposes of misfolded alpha-1 proteins. Shujuan Pan, PhD, of Sifers’ research team leads most of these efforts.

When Alpha-1 babies get liver disease, Rick Sifers blames it on ERMan1.

In Alphas, mutant forms of the alpha-1 protein (AAT) misfold in the liver. The misfolded protein can’t be transported normally out of the liver cell, which can lead to both lung and liver disease. The AAT tends to accumulate in the liver. In some Alphas, this happens so fast they have liver disease when they’re newborn.

“What’s behind all this, Sifers says, is ER Mannosidase 1 (or ERMan1). “ERMan1 is the key regulator in the protein degradation process,” he says. “It’s a fact that escaped researchers for years because it exists at very low concentration in cells.”

A mannosidase is an enzyme that removes mannose from proteins in the body – it strips the sugar molecule from glycoproteins such as the alpha-1 protein. (Mannose is a form of sugar; the word is derived from manna, the food eaten by the Israelites in the Old Testament.) The removal of the sugar molecule seems to be the essential first step in disposing of AAT.

Sifers’ research team is studying a mutation called a “single nucleotide polymorphism” or SNP (pronounced “snip”) in the gene for ERMan1. The studies include DNA extracted from liver tissue from the Alpha-1 DNA and Tissue Bank. “This mutation doesn’t cause liver disease, but it is responsible for accelerating the process so that it shows up in the infant and toddler population (before four years of age).”

“This is something I hypothesized 20 years ago.
— because Alpha-1 liver disease is caused [at least in part] by a buildup of protein in the liver, I reasoned that there might be a defect in the protein degradation process in some people. A lot of my fellow researchers questioned my logic."

Now, odd as it sounds after 20 years, “We are just at the beginning of the investigation process,” Sifers says. “Despite the success in identifying a modifier of the liver disease, the work is far from over because the underlying cause of the actual disease is still not understood. But I’m convinced we’re on the right track.”

He sees the next step as an effort to exhaustively compare [both genetically and biochemically] more members of the protein degradation process in Alpha-1 patients who develop liver disease with those who don’t.

Sifers hopes this research will eventually find a way to predict which Alpha-1 patients will develop liver disease — and then lead to development of a cure.

Rubin Tuder, MD, Hart Family Professor of Medicine and Pathology, Director, Program in Translational Lung Research, University of Colorado, Denver, is studying excessive cell death in the lungs of people with COPD. Rubin Tuder is fascinated by the way cells die in a living human body — and especially why researchers find increased numbers of dead cells, particularly in disease.

Tuder is studying accelerated apoptosis in the lung. Apoptosis [derived from the Greek word referring to “falling leaves”) is a form of cell death. When cell death occurs because of a natural process it is also called programmed cell death, or PCD.

Toes and fingers, for example, are formed by PCD. While a human embryo develops, cells die in the hands and feet, removing the tissue between the digits. In the adult body, some cells are always dying, being digested and disposed of.

This normal process happens too rapidly in some diseases, such as those that damage the lungs of Alphas. “Six years ago, we started addressing apoptotic destruction in emphysema,” Tuder says. “We documented this process in animal models and the lungs of human smokers.” A new question is drawing Tuder’s attention: the possibility that removal of these cells is also abnormal in Alphas, causing the cells to remain for prolonged periods.

What causes cells to die too rapidly?

A major culprit could be caspases, enzymes that chew up proteins. They play a central role in both cell death and inflammation. Caspase 3 is an “executioner caspase” being studied by Tuder. Animal models demonstrate that blocking the Caspase 3 system could delay or block apoptosis, says Tuder.

Alpha-1 protein (AAT) can act as an “anti-aptotic agent,” he says. “AAT binds to Caspase-3 and blocks it.”

Tuder’s work suggests that AAT may block excessive cell death by a unique process — separate from the protein’s qualities of reducing inflammation and controlling neutrophil elastase, the enzyme blamed for destruction of lung tissue in COPD.

Tuder is using tissue from explanted lungs [removed from the human body, typically in the course of lung transplant surgery] in his research, including lung tissue from the Alpha-1 Tissue Bank. [1]
Four boards hold joint meeting, make history

The boards of four organizations with complementary missions met jointly in a first-time-ever event in Miami this year. The boards of the Alpha-1 Foundation, Alpha-1 Association, AlphaNet and the COPD Foundation met Feb. 8 and discussed their intertwined goals and priorities.

Stew Cogan, Esq., an original board member of the Alpha-1 Foundation, spoke on “Board Fiduciary Responsibilities” and facilitated the day’s discussions.

Among the key challenges addressed were confusion of the roles of each organization by both the community and industry, and a discussion on how to increase collaboration among the Alpha-1 Foundation, Alpha-1 Association, AlphaNet and Alpha-1 Kids. The latter organization also had representatives at the meeting.

To top off the day, everyone was invited to the Alpha-1 Foundation Donor Recognition Dinner that evening.

Adam Wanner, MD, the Foundation’s Scientific Director, and Jeffrey Teckman, MD, Associate Professor of Pediatrics at St. Louis University School of Medicine and a veteran researcher on Alpha-1 liver disease, spoke on the current state of research in Alpha-1 lung and liver disease.

Among those honored for longtime leadership in the Alpha-1 community:

— Sarah E. (Sally) Everett, Esq., an original Foundation board member, received the Stew Cogan Governance Award for Distinguished Service in Ethics and the Law. Adding a warm touch to the evening, she received the award from Stew Cogan himself.

— Gerard M. (Jerry) Turino, MD, Senior Professor of Medicine at the Mara Center, St. Luke’s/Roosevelt Hospital in New York. Turino has been researching Alpha-1 and COPD for decades. He chairs the COPD Foundation board, heads the Alpha-1 Community Advisory Committee and serves on the Foundation’s Medical and Scientific Advisory Committee as well as its Clinical Resource Centers and Grants Advisory committees.

— Robert J. (Bob) Haggerty for many years secretary and board member of the Alpha-1 Association, for his “exemplary leadership, distinguished service and his commitment to the Alpha-1 community.”
Researchers look at the past, present and future of aerosolized augmentation therapy.

Alphas, how would you like to puff on a nebulizer for a few minutes once or twice a day, and give up the IV needles and infusions for your Alpha-1 augmentation?

Sounds pretty good? Simple? Convenient? Well, the idea seems simple enough. The devil has been in the details.

The Alpha-1 Foundation has been working on inhaled therapy for more than 10 years. Initially, the biggest impediment to progress was the exorbitant licensing fee structure, says John Walsh, Foundation President and CEO. The National Institutes of Health (NIH) Office of Technology Transfer was not actively helping to negotiate lower fees with pharmaceutical companies, and that made testing and research too expensive. The Foundation met with Sen. Orrin Hatch, then Chairman of the Senate Judiciary Committee, and soon things changed for the better. But there were other hurdles to clear.

“We’ve had a few disappointments and some false starts with aerosolized delivery of AAT,” says Walsh. “But we’ve continued to make it a priority and we have no qualms about hammering away at anyone who will listen. Israeli pharmaceutical company Kamada has finished a phase-1 trial with aerosolized delivery of AAT for cystic fibrosis (CF) patients, and is scheduled to do another trial for Alpha-1 patients. And Talecris Biotherapeutics now has a very aggressive aerosol development program under way.”

For inhaled therapy to become reality, a few things need to — and are beginning to — fall into place.

Multi-talented molecule
The alpha-1 molecule (AAT) seems to be multi-talented. It was long accepted that AAT is an antiprotease — it blocks the potentially destructive actions of enzymes. But it does more.

“Most researchers in the field now believe that AAT is a broad-spectrum anti-inflammatory molecule made by Mother Nature,” says Mark Brantly, MD, director of the Alpha-1 Research Program at the University of Florida College of Medicine. “So any kind of lung disease associated with inflammation may be a reasonable target for therapy. That’s a really good thing.” Because aerosolized AAT may be five to 10 times more efficient than IV augmentation for lung diseases, Brantly says, a larger potential market is critical to drug companies — so they can see a market for the product that justifies the development cost.

“There are data that inhaled AAT can have anti-inflammatory benefits in CF patients,” said noted researcher Robert Stockley, MD, Queen Elizabeth Hospital, Birmingham, England. “I’ve been trying to persuade companies to look into this for 10 years.” Because aerosolized AAT may be five to 10 times more efficient than IV augmentation for lung diseases, Brantly says, a larger potential market is critical to drug companies — so they can see a market for the product that justifies the development cost.

“Emphysema results from destruction of elastin fibers in the lung. These fibers are located around the air sacs in the interstitium — between the air sacs and the blood vessels — and make up the structural scaffolding in the lung.
How much and where?
So, if you develop an aerosol that reaches the air sacs, does it also reach the interstitium? Brantly believes the answer is yes. “We’ve demonstrated in a number of experiments that aerosolized AAT appears in the lymph and in the blood after being inhaled,” he says. “This indicates that it does transfer. And in theory, that would protect against elastin degradation.”

Says Stockley: “If you want to prevent or stop the progression of emphysema, you need specific inhalation methodologies that ensure you get particles of the right size to make it into the air sacs. There are a variety of companies looking at the nebulized route right now. As long as we are using human protein, as opposed to transgenic protein, then I believe we will minimize the problems.”

Studies are under way to determine whether delivery systems are adequate, whether the protein can be purified enough to avoid potential toxicity, and what doses might be useful for various health conditions.

Getting there
To win FDA approval, a product needs to be proved safe and effective. Pulmonary function tests (PFTs — “Blow! Keep blowing!”) have long been the standard for demonstrating effectiveness of drugs for lung diseases. The variable nature of PFTs means more study subjects are needed for a longer period of time. That makes the study very expensive. “For most clinical trials” Brantly explains, “it could cost up to $80,000 per subject per year. Now we’re looking at a faster, more precise way of measuring success in a clinical trial: CT scanning.”

CT scanning promises to be a faster and more accurate way to assess the progression of lung disease (See story on CT Scan Workshop, page 3). When the analysis of CT scanning becomes standardized, it will open the door to shorter, less expensive studies.

“Right now we’re coming to a confluence” said Brantly. “We’re developing the devices. We have highly purified forms of AAT available, and robust clinical evaluation tools are coming into focus real soon. We’ve got the patients to do the studies. We will be doing phase-1 and phase-2 studies with several companies in the near future. If I had to guess, I’d say we’ll probably have aerosolized AAT for the Alpha-1 population in about three years if all goes right.”

Brantly quips: “I promised John Walsh I’d have it done by the end of the decade. Now that I’ve made the commitment, we all have to work very hard to make it happen.”
In his new role at the University of Massachusetts, Dr. Terence Flotte sees an opportunity to advance Alpha-1 gene therapy research.

W hen Terence R. Flotte, MD, moved from Florida to Massachusetts, he didn’t do it because of the weather. The move empowered him to take a promising gene therapy research program to new heights.

Flotte, previously Chair of the Department of Pediatrics at the University of Florida, is now Dean of the School of Medicine at the University of Massachusetts. In his new post, he believes he can shepherd the genetic therapy research he has worked on for more than 10 years in exciting new ways.

“An important element of what we’re doing in the lab is to find ways to knock down mutant AAT protein in the liver while retaining the ability to deliver the normal protein to the liver and elsewhere,” Flotte said. “The knockdown strategy that has proven most effective is based on a mechanism called RNA interference (RNAi).”

RNAi blocks the expression of specific genes. UMass has been the epicenter of RNAi research since the school’s Dr. Craig Mello won a Nobel Prize for his groundbreaking work published in 1998.

“UMass Medical School is really a prominent hub of RNAi activity,” Flotte said. “In addition, Governor Deval Patrick has shown tremendous leadership in putting forward life sciences as a major priority.”

Flotte’s own Alpha-1 study goes back to 1998, when he published papers on the delivery of normal alpha-1 antitrypsin [AAT] protein through muscle tissue. The idea was to inject AAT into muscles in the arm and have the muscle tissue express the DNA, creating an alternative to the liver as a source for normal alpha-1 protein. The initial study funded by the National Institutes of Health (NIH) was performed on mice.

A human study, funded by the NIH and Applied Genetic Technologies, is in its second generation. It uses a newly-developed viral envelope to deliver the gene. Volunteers in this study receive a series of nine injections in a grid. Ultrasound is used to make sure the injection does not take place near a blood vessel. The results, says Flotte, are very promising. A report is tentatively scheduled to be released in detail at the American Society of Gene Therapy Annual Meeting in Boston at the end of May.

Besides greater control over all aspects of the research, Flotte explains other benefits of his move to UMass. “We’ve seen a number of tremendous opportunities coalesce here. We’ve combined three research areas — gene therapy, RNAi and stem cell research — into one cluster. It will be housed in a new half-million-square-foot facility on campus, scheduled to be completed by 2011. We will recruit 40 new investigators and are in the process of initiating a human embryonic stem cell bank here. Since it is funded by the state, it can use approved and non-approved stem cell lines. And we will institute a national stem cell registry.”

The mission of the research cluster will be broad, including a whole range of diseases from emphysema to cancer. Flotte’s own work on Alpha-1 will benefit greatly, he said. And in his role as dean, he will work with the university’s chancellor to map out a strategic plan for the next five or 10 years.

The main idea is to speed the transition from basic research to clinical practice. “Being able to fundamentally alter the way an academic medical center approaches research is something one rarely gets,” Flotte said. “UMass is at a point in its maturation where it was ready to make an enormous investment in advanced therapeutics. The fit between me and what they were looking for was perfect. It will allow me to put in place the vision that my colleagues and I have had since we began our work.”
COPD resource kits spread the word about the need for Alpha-1 testing

One way to make sure more people—and the right people—know about Alpha-1 testing is to put the information directly into the hands of the healthcare professionals who deal regularly with Chronic Obstructive Pulmonary Disease (COPD), as well as the caregivers of those with COPD. That’s where the COPD Foundation’s resource kits come in handy.

The COPD Resource Kit was developed as part of the National Heart, Lung & Blood Institute (NHLBI) Learn More Breathe Better Campaign. The kit includes handouts for medical professionals, a multimedia CD-ROM, and an educational video.

“The fact that the Alpha-1 Foundation gave a grant to the COPD Foundation to develop the Learn More Breathe Better Campaign—including the development of these valuable resource kits—is significant,” said Alpha-1 Foundation President and CEO John W. Walsh. “Information about testing for Alpha-1 is mentioned in the kit. And to be able to co-brand with NHLBI and have their endorsement is very important.”

The kit for professionals is available through www.learnaboutcopd.org. For family and caregivers of COPD patients, Dey LLP has developed a kit available through the COPD Foundation’s COPD Information Line, 1-888-316-2673.

A friend in Congress


“The Congresswoman has been a valued friend for years, and we applaud her elevation to this vital position in Congress,” said John W. Walsh, President and CEO of the Alpha-1 Foundation and President of the COPD Foundation. “It’s wonderful to see her in a leadership role in the Organ and Tissue Donation Caucus.”

Robert A. Sandhaus, MD, PhD, clinical director of the Alpha-1 Foundation, said Ros-Lehtinen “has spearheaded efforts in Congress to end genetic discrimination, and her role in the Organ and Tissue Donation Caucus will help to assure stronger efforts toward greater availability of life-saving organ transplants.”

Come to the Conference

The 2008 Alpha-1 Association Conference will be better than ever.

Frank Deford, noted writer and commentator, will give the keynote address at the Alpha-1 Association’s 17th Annual National Education Conference on June 20-22 in St. Louis, MO.

Deford is a correspondent for the popular HBO television show RealSports with Bryant Gumbel, and did a segment for the show last November with Alpha Len Geiger, who received a lung transplant in 2002, and Kevin and Kristie Shroyer, the parents of Geiger’s lung donor, Korinne Shroyer. Deford mentioned on the show that he himself is an Alpha. Deford is also a weekly commentator for NPR Radio’s Morning Edition, Senior Contributing Writer for Sports Illustrated, and the author of several books.

John W. Walsh, President and CEO of the Alpha-1 Foundation, will talk about “Working Together to Find a Cure,” and Adam Wanner, MD, the Foundation’s scientific director, will discuss the Foundation’s new “State of the Cure” document. Other speakers include Jeffrey Teckman, MD, who will talk about potential breakthroughs in Alpha-1 liver research, and David Lomas, MD, PhD, of Cambridge University in England who will discuss potential breakthroughs in Alpha-1 lung research.

Saturday’s lunch will feature “Meet the Experts,” when participants will get a chance to eat and talk with experts on Alpha-1 lung and liver disease as well as organ transplants. Breakout session topics will include pulmonary rehabilitation, oxygen therapy, lung and liver transplants, and coping for Alpha-1 parents.

The conference registration deadline is June 5. For a discounted hotel rate, please make reservations at the Sheraton Westport Plaza by May 18.

For conference reservations or details, call toll-free 1.800.521.3025 or visit www.alpha1.org.
Food is Love

Barbara Kushner talks of Emeril Lagasse’s gesture to honor her husband’s memory.

When my husband John Kushner passed away in the summer of 2005, some very special and supportive people came to show their respects. Among them were Emeril Lagasse and some of Emeril’s colleagues. There they were, these wonderful people, at my house in New Orleans, bringing food and condolences.

Before Emeril opened his own restaurant, he’d been head chef at Commander’s Palace, a legendary dining establishment in the New Orleans Garden District. John, being in commercial real estate, would go there often and Emeril would always come out and say hello. John would always order a particular chocolate soufflé. When Emeril eventually opened his own restaurant, J.K.’s Chocolate Soufflé became a regular item on the menu. J.K., of course, was John Kushner.

John would become great friends with Emeril. He helped Emeril find many of the locations for his restaurants, including the one in Miami Beach, at 1601 Collins Avenue. And on May 18, Emeril will reserve that incredible restaurant for a benefit honoring John. Proceeds from the event will go to the Alpha-1 Foundation, via the John E. Kushner Family Fund.

Of course, the food will be fantastic. And so many friends, business relations and members of the Alpha-1 community have asked to be a part of it, we’ll probably have to turn away three times as many people as we seat. The money we raise from the dinner and the silent auction will go toward Alpha-1 education and awareness.

My family and I have been throwing ourselves into this event for some time. This involvement has helped me heal. And I can’t begin to express my appreciation and admiration for everyone who’s helped make it come true.

It’s very touching that, years later, Emeril and his people are still there for us — still bringing food and condolences. I guess it’s just what good friends do. Thank you.

Emeril’s Demi J.K. Soufflé

Ingredients:
Butter for ramekins; ½ cup sugar, plus extra to coat ramekins; 4 eggs, separated; 2 tablespoons Grand Marnier; 6 ounces chocolate, melted; confectioners’ sugar, for dusting; ½ cup chocolate sauce, for serving

Instructions:
Preheat oven to 400 degrees. Brush 4 small ramekins with butter, making sure to coat thoroughly, including rims. Coat completely with sugar, gently tapping out any excess. In a mixing bowl, whisk yolks, ¼ cup of sugar, and Grand Marnier until thoroughly mixed. Stir in melted chocolate. In another bowl, beat egg whites to soft peaks, add remaining sugar and beat just until stiff. Add half of whites to chocolate mixture, stirring thoroughly, including rims. Coat completely with sugar, gently tapping out any excess. In a mixing bowl, whisk yolks, ¼ cup of sugar, and Grand Marnier until thoroughly mixed. Stir in melted chocolate. In another bowl, beat egg whites to soft peaks, add remaining sugar and beat just until stiff. Add half of whites to chocolate mixture, stirring to lighten mixture, and incorporate completely. Gently fold in remaining whites, keeping batter light as you can. Some white streaks may remain. Spoon batter into prepared ramekins. Bake 8 to 10 minutes until puffed. Serve immediately, dusted with confectioners’ sugar, and pass warm chocolate sauce at table.

Yield: 4 servings

Recipe from New New Orleans Cooking, by Emeril Lagasse and Jessie Tirsch
Calendar of Upcoming Events

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 15</td>
<td>Get the Scoop on Alpha-1: Ice Cream Fundraiser</td>
<td>Denver, CO</td>
</tr>
<tr>
<td>May 16</td>
<td>Alpha Okies Silver Horne Golf Event</td>
<td>Oklahoma City, OK</td>
</tr>
<tr>
<td>May 18</td>
<td>Emeril Lagasse’s Tribute to John E. Kushner</td>
<td>Miami Beach, FL</td>
</tr>
<tr>
<td>May 18</td>
<td>Fraternal Order of Eagles Golf Tournament</td>
<td>Gainesville, FL</td>
</tr>
<tr>
<td>May 30–June 1</td>
<td>Weekend in Paradise Golf &amp; Fishing Invitational Tournament</td>
<td>Key Largo, FL</td>
</tr>
<tr>
<td>June 8</td>
<td>Breath of Life Cocktail Reception</td>
<td>Greenwich, CT</td>
</tr>
<tr>
<td>June 15</td>
<td>Fathers Day Campaign</td>
<td>Internet</td>
</tr>
<tr>
<td>June 27–29</td>
<td>Breathe Easy Bike Ride</td>
<td>Santa Inez, CA</td>
</tr>
<tr>
<td>July 11–16</td>
<td>U.S. Transplant Games</td>
<td>Pittsburgh, PA</td>
</tr>
<tr>
<td>July 26</td>
<td>Plymouth Harbor Cruise</td>
<td>Plymouth, MA</td>
</tr>
<tr>
<td>Sept. 12–14</td>
<td>ALA Escape to the Cape Team Alpha-1 Teams</td>
<td>Cape Cod, MA</td>
</tr>
</tbody>
</table>

For fundraising event information, contact Angela McBride at 888.825.7421 ext. 233 or amcbride@alphaone.org, for an application. Talecris Biotherapeutics is the anchor sponsor for the Team Alpha-1 Program.

Bijoux by Betties

These elegant necklaces (that’s the “Venus” model at left, the “Athena” at right) of 14-carat-gold-filled pieces and gemstones including amethyst, blue topaz, citrine and fresh-water pearls, are available from the Alpha Betties group to raise funds for Alpha-1 Foundation research and programs. For information call Linda Rodriguez at 888.825.7421 Ext. 237 or lrodriguez@alphaone.org.

Register Now!

It’s so easy!
If you’ve been diagnosed with Alpha-1 or identified as a carrier, we need you. Register today, become a part of the Alpha-1 Research Registry, and you’ll be on the leading edge for new therapies and research. Alphas helping Alphas – together, we will find a Cure.

For more information about the Alpha-1 Research Registry, please call our toll free number 1-877-886-2383 or contact us by email at alphaone@musc.edu.
"I was very lucky."

AlphaNet coordinator Sandy Singleton has made helping others a way of life.

It was a fluke that Sandy Singleton was diagnosed with Alpha-1. In 1995, at age 43, she was working as a medical transcriber in a pulmonologist’s office. When she began to feel recurring numbness in her hands, she thought it was carpal tunnel syndrome. Her pulmonologist boss had a different perspective and suspected a lung problem. So without exhibiting any of the usual symptoms of Alpha-1, she was tested and diagnosed with the condition.

"I was very lucky," Singleton said. "I did not experience the horror stories that sometimes are associated with Alpha-1."

It wasn’t until she attended a support group meeting three years later that she realized everyone else there was on augmentation therapy except her. That’s when she began taking Prolastin. "I’ve lost about 10 percent of my lung function in 13 years," she says.

A native Californian, Singleton makes her home in Ashland, Oregon — a comfortable college town. She and her dog, Bentley, walk about two hours a day. The pair also spend time at the local nursing home once a week, visiting the residents and putting smiles on faces there.

Brand New Brand Name

Contest winner Gayle Allison Tipper returns from her trip to Israel.

AlphaNet coordinator Gayle Allison Tipper read about Kamada’s brand naming contest in Alpha-1-To-One magazine last year and decided she’d give it a try. She was pretty busy when the contest deadline rolled around, though. She was in Gainesville, FL, with her husband, Larry, where she was participating in a study for Kamada’s IV augmentation product – the product with the naming contest. She remembered the deadline, and spent a few minutes online submitting what turned out to be the entry that won her and her husband a trip to Israel.

"I came up with the name Allset because the product didn’t have to be mixed," Tipper said. "It was all set and ready to go."

The trip began in Tel Aviv, where the Tippers were treated to dinner in a fashionable restaurant on the Mediterranean Sea. Then on to Jerusalem, where they visited the Mount of Olives and toured the Kamada plant and its neighboring kibbutz.

"The tour of the Dead Sea and Masada was breathtaking," Tipper said. "It was the most beautiful scenery I have ever seen. It was a great trip, and my husband and I plan to go back in a few years."

The second-place entry was "Everlife" from Cathy Gould and third place was "Alfair" from Diane Abuelo, MD. Kamada can’t be certain of the final name of the product until it completes the complex legal and regulatory processes of brand-naming.
DESCRIPTION
Alpha1-Proteinase Inhibitor (Human), Prolastin® is a sterile, stable, lyophilized preparation of purified human Alpha1-Proteinase Inhibitor (alpha1-PI), also known as alpha1-antitrypsin deficiency is a chronic, hereditary, usually fatal, autosomal recessive disorder in which a low concentration of alpha1-PI (alpha1-antitrypsin) is associated with slow, progressive, severe panacinar emphysema that most often manifests itself in the third to fourth decades of life. Although the terms “Alpha1-Proteinase Inhibitor” and “alpha1-antitrypsin” are used interchangeably in the scientific literature, the hereditary disorder associated with a reduction in the serum level of alpha1-PI is conventionally referred to as “alpha1-antitrypsin deficiency.” The emphysema is typically worse in the lower lung zones. The pathogenesis of development of emphysema in alpha1-antitrypsin deficiency is not well understood. However, alpha1-antitrypsin is a chronic, biologically active inhibitor of elastase, an enzyme capable of degrading elastin tissues, released by inflammatory cells, particularly neutrophils in the lower respiratory tract, resulting in progressive destruction of lung tissue. The eventual outcome is the development of emphysema. Neonatal hepatitis with cholestatic jaundice appears in approximately 10% of newborns with alpha1-antitrypsin deficiency. In some adults, alpha1-antitrypsin deficiency is complicated by cirrhosis, A large number of phenotypic variants of alpha1-antitrypsin deficiency exists. The most severely affected individuals are those with the PiZZ variant, typically characterized by alpha1-PI serum levels <35% normal. Epidemiologic studies of individuals with various phenotypes of alpha1-antitrypsin deficiency have demonstrated that individuals with endogenous serum levels of alpha1-PI ≤50 mg/dL (based on commercial standards) have a risk of >80% of developing emphysema over a lifetime. However, with alpha1-PI levels >100 mg/dL, in general, no risk of emphysema was noted. In these studies, it was observed that the “threshold” level of alpha1-PI in the serum required to prevent or delay development of emphysema with alpha1-antitrypsin deficiency is approximately 80 mg/dL (based on commercial standards for immunoassay of alpha1-PI).

In clinical studies of Prolastin, 23 subjects with the PiZZ variant of congenital deficiency of alpha1-antitrypsin participated in a study of acute and/or chronic replacement therapy with Prolastin. The mean in vivo recovery of alpha1-PI was 4.2 mg (immunologic)/dL per mg (functional)/kg body weight administered. The half-life of alpha1-PI in vivo was 150 minutes. Based on these results, a protocol of one injection of Prolastin every 4 weeks was employed to maintain a therapeutic level of alpha1-antitrypsin. A group of individuals who participated in the investigations were immunized with Hepatitis B Vaccine and received a single dose of Hepatitis B Immune Globulin (Human) on entry into the investigation. Although no other steps were taken to prevent hepatitis, neither hepatitis B nor non-A, non-B hepatitis occurred in any of the subjects. All subjects remained seronegative for HIV antibody. None of the subjects developed any detectable antibody to alpha1-PI or alpha1-antitrypsin. Long-term control clinical data are available to evaluate the effect of chronic replacement therapy with Prolastin on the development or progression of emphysema in patients with congenital alpha1-antitrypsin deficiency have not been performed. Estimates of the sample size required to detect a 15% slope change and the slow, progressive nature of the clinical course have been considered impediments in the ability to conduct such a trial. Studies to monitor the long-term effects will continue as part of the postapproval process.

INDICATIONS AND USAGE
Prolastin is indicated for chronic replacement therapy of individuals having congenital deficiency of alpha1-PI (alpha1-antitrypsin deficiency) with clinically-acceptable alpha1-antitrypsin. Clinical and biochemical studies have demonstrated that with such therapy, it is possible to increase plasma levels of alpha1-PI, and that levels of functionally active alpha1-PI in the lung epithelial lining fluid are increased. As some individuals with alpha1-antitrypsin deficiency will not go on to develop panacinar emphysema, only those with evidence of such disease should be considered for chronic replacement therapy. In the PiZZ and PiMZ genotypes of alpha1-antitrypsin deficiency should not be considered for such treatment as they appear to be at small risk for panacinar emphysema. Clinical data are not available as to the long-term effects derived from chronic replacement therapy of individuals with alpha1-antitrypsin deficiency with Prolastin. Only adult subjects have received Prolastin to date. Prolastin is not indicated for use in patients other than those with PiZZ, PiM(Z) or PiM(SZ) phenotypes.

CONTRAINDICATIONS
Individuals with selective IgA deficiencies who have known antibody against IgA (anti-IgA antibody) should not receive Prolastin, since these patients may experience severe reactions, including anaphylaxis, to IgA which may be present.

WARNINGS
Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent. The risk that such agents can still potentially be transmitted is remote. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. All infections thought by a physician possibly have been transmitted by this product should be reported by the physician or other healthcare provider to Telecris Biotherapeutics, Inc. [1-800-520-2820].

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to a patient.

CONTRAINDICATIONS
1. Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.
2. Administer only by the intravenous route.
3. As with any colloidal solution, there will be an increase in plasma volume following intravenous administration of Prolastin. Caution should therefore be used in patients at risk for circulatory overload.
4. Prolastin should be given alone, without mixing with other agents or diluting solutions.
5. Product administration and handling of the needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious virus including HIV and hepatitis. Obtain immediate medical attention if such occurs. Place needles in sharps container after single use. Discard all equipment including any reconstituted Prolastin product in accordance with biohazard procedures.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals to evaluate carcinogenicity, mutagenesis, or impairment of fertility have not been conducted.

Pregnancy Category C
Animal reproduction studies have not been conducted with Prolastin. It is also not known whether Prolastin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Prolastin should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether Prolastin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prolastin is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS
Therapeutic administration of Prolastin, 60 mg/kg weekly, has been demonstrated to be well tolerated. In clinical studies of Prolastin, 0.7% of subjects experienced a reaction consistent with an allergic (hypersensitivity) reaction. None of the reactions was severe. The adverse reactions reported included delayed fever (maximum temperature rise was 38.8°C, resolving spontaneously over 24 hours) occurring up to 12 hours following treatment (0.7%), light-headedness (0.19%), and dizziness (0.19%). Mild transient leukocytosis and dialysis anemia several hours after infusion have also been noted. Since market entry, occasional reports of urticarial-like symptoms, allergic reactions, chills, dyspnea, rash, tachycardia, and, rarely, hypotension have also been received. Rare cases of transient increase in blood pressure or hypotension and chest pain have also been reported.

DOSE AND ADMINISTRATION
For INTRA-VENOUS USE ONLY
Each bottle of Prolastin has the functional activity, as determined by inhibition of porcine pancreatic elastase, as stated on the label of the bottle. As expressed as actual functional activity, i.e., actual capacity to neutralize porcine pancreatic elastase, the “threshold” level of alpha1-PI in the serum believed to provide adequate anti-elastase activity in the lung of individuals with alpha1-antitrypsin deficiency is 80 mg/dL (based on commercial standards for alpha1-PI immunologic assay). However, assays of alpha1-PI based on commercial standards measure antigenic activity of alpha1-PI, whereas the labeled potency value of alpha1-PI, Prolastin is expressed as actual functional activity, i.e., actual capacity to neutralize porcine pancreatic elastase. As expressed as actual functional activity, alpha1-PI measured using commercial immunologic assays may not accurately reflect actual functional alpha1-PI levels. Therefore, although it may be helpful to monitor serum levels of alpha1-PI in individuals receiving Prolastin, using currently available commercial assays of antigenic activity, results of these assays should not be used to determine the required therapeutic dosage. The recommended dosage of Prolastin is 60 mg/kg body weight administered once weekly. This dose is intended to increase and maintain a level of functional alpha1-PI in the epithelial lining of the lower respiratory tract, providing adequate anti-elastase activity in the lung of individuals with alpha1-antitrypsin deficiency. Prolastin may be given at a rate of 0.08 mL/kg/min or greater and must be administered over 30 minutes. It is recommended that the dose be adjusted to achieve the desired peak concentration to infuse.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Safety and effectiveness in pediatric patients has not been established.

STORAGE
Prolastin should be stored at temperatures not to exceed 25°C (77°F). Freezing should be avoided as breakage of the diluent bottle might occur.
With PROLASTIN, you get more than just a leading alpha-1 treatment. You also get the leader in alpha-1 care—PROLASTIN DIRECT.*

1.800.305.7881

One simple call provides easy access to:

• Health management from AlphaNet
• Insurance reimbursement help
• Customized drug delivery and home infusion
• Prompt answers to questions about PROLASTIN therapy

Plus, PROLASTIN DIRECT is fully staffed by alpha-1 specialists, many of whom are alphas themselves, so they understand firsthand that there’s more to successful treatment than first-rate infusions.

IMPORTANT SAFETY INFORMATION
PROLASTIN is for people who have emphysema caused by inherited alpha-1-antitrypsin deficiency. In clinical trials of PROLASTIN, side effects were not common and occurred in 1.16% of weekly infusions. Side effects were generally mild with the most common being fever, light-headedness, and dizziness. Individuals with selective IgA deficiencies should not receive PROLASTIN. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. As with all plasma-derived products, the potential to transmit infectious diseases cannot be totally eliminated.

Please see brief summary of PROLASTIN full Prescribing Information on adjacent page.

*Formerly known as Talecris Direct®.

©2008 Talecris Biotherapeutics, Inc. All rights reserved. Printed in USA April 2008 PR42-0308
www.prolastin.com