

# Medicines for Life<sup>®</sup>



United Therapeutics Corporation 2002 Annual Report

# Corporate Profile

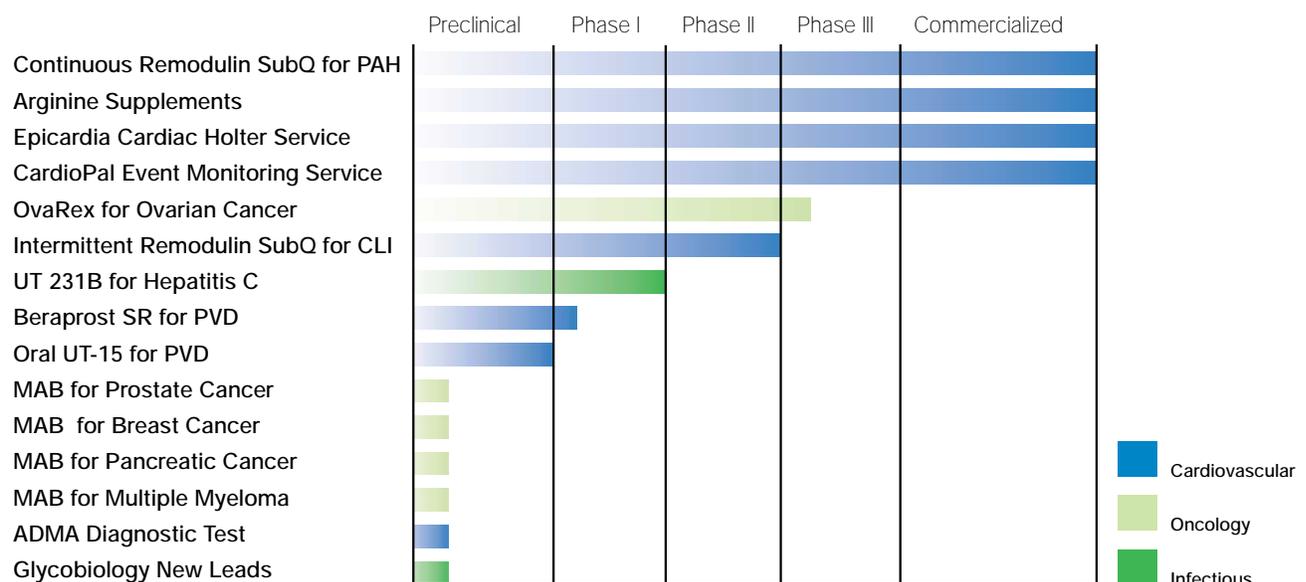
The medical artwork on the cover is a thousand word picture of what United Therapeutics is all about. We are a cardiovascular company. We have begun the necessary spade work to one day also offer medicines that combat cancer and infectious diseases. For now, though, our revenue-generating products are all in the field of cardiovascular medicine.

Our lead product and largest revenue earner, Remodulin, is approved in the United States, Canada, and Israel for pulmonary arterial hypertension (PAH). This life-threatening disease results from the pulmonary arteries becoming dysfunctional, resulting in right heart failure if not adequately treated. Remodulin is also being tested by us in randomized, placebo-controlled studies for critical limb ischemia (CLI). This disease, which afflicts millions of people, results from atherosclerosis of the cardiovascular system, resulting in severe leg pain and non-healing ulcers, eventually requiring limb amputation. Remodulin also has remarkable inotropic properties, meaning that it helps the heart muscle pump blood more efficiently. Consequently, there is also considerable interest in the development of Remodulin for congestive heart failure (CHF).

Telecardiology services approved for health care reimbursement for patients with an array of possible cardiac arrhythmias are our next largest revenue earner. Our CardioPAL product is the most technologically advanced portable heart monitor in the industry. Our EpiCardia service provides cardiologists with a printed ECG report on their patients anywhere in the United States as quickly as one hour after the patient connects our device to a telephone receiver. We are working on developing yet more sophisticated telecardiology technology, including devices that can provide valuable information on atrial as well as ventricular fibrillation and devices that automatically detect silent arrhythmias.

A third revenue earner for us in the field of cardiovascular health is our arginine supplementation business. Arginine is one of the twenty amino acids necessary for life. In our bodies, enzymes convert arginine into nitric oxide. This conversion is crucial for the health of the endothelial linings along our 100,000 kilometers of blood vessels and capillaries. United Therapeutics is the exclusive licensee of several Stanford University patents covering the use of arginine for the promotion of vascular function.

## Product Pipeline – 15 Products



Last updated March 2003. The successful development of this Product Pipeline is subject to risks and uncertainties such as those described in United Therapeutics' periodic reports filed with the Securities and Exchange Commission.

Cardiovascular medicine is a good place for United Therapeutics to be. There are two reasons why we believe we can provide more benefits in this therapeutic area than in any other market segment. First, our products are strong leaders in this market. More than seventy-five percent of doctors who treat significant numbers of pulmonary hypertension patients now prescribe Remodulin. Our telecardiology devices are the smartest, smallest products in the industry. The strength of our arginine intellectual property portfolio was demonstrated this past year when the largest company in the field chose to accept a licensing agreement from us. The second reason cardiovascular medicine is a good market segment for United Therapeutics is because it is the largest health care market. More people succumb to cardiovascular disease than to any other illness in America, as well as in Europe, China, and India.

While building our company's business value in the cardiovascular field, we are also laying important foundations for future franchises in oncology and infectious diseases. We are undertaking the largest ever pivotal trials of a potential medicine for preventing the recurrence of ovarian cancer. In addition, this medicine is part of a family of similar therapies to which United Therapeutics owns the rights and which are designed to combat prostate, breast, lung, pancreatic, colorectal and multiple myeloma cancers.

In the field of infectious disease, we are targeting hepatitis C and other diseases with unique glycobiology compounds discovered by the field's founder, Professor Raymond Dwek of Oxford University. While this work is at an early stage, with safety testing in patients underway, it holds immense promise. The diseases being targeted afflict over a billion people worldwide, and the compounds are part of an entire new class of pharmacological agents.

United Therapeutics has been singularly successful at developing therapies with a comparatively low cash burn rate as compared to other public biotechnology companies. We accomplish this by working efficiently and by outsourcing our pre-clinical research efforts to major academic centers whenever feasible. Another major factor in our success has been our control over manufacturing, with a company-owned facility that produces our lead product. We are also efficient in the sales and marketing arena by virtue of partnerships with half a dozen drug distribution and detailing firms. These partnerships are complemented by in-house commercialization professionals and our commitment to providing doctors and patients with accurate information and ongoing research related to our products.

The heart and lungs are remarkable organs. Perhaps more than any other word, "balance" describes what they do. Their excellence at balancing blood flow and gas exchange is far more marvelous than any machine man has yet devised. As a company, we, too, aspire to balance. Our balanced approach to cardiovascular medicine includes a pharmaceutical (Remodulin), a diagnostic (telecardiology) and a nutraceutical (arginine). Our cardiovascular drug development strategy is balanced with a commercialized use (PAH), a well-understood but not yet approved use (CLI), and a novel use (CHF). And our overall company strategy is balanced among mature programs (cardiovascular), pivotal development (oncology), and early-stage pipeline activities (infectious disease).

In addition to balance, the heart also symbolizes vitality and caring. At United Therapeutics, we find tremendous inspiration for our work and view our products as being "new beginnings" for patients and doctors, with quality of life as our utmost therapeutic goal.



# To Our Shareholders



## Senior Management

(Pictured left to right)

**David Walsh, Ph.D.,**  
Executive Vice President and  
Chief Operating Officer,  
Production

**Yu-Lun Lin,**  
President and  
Chief Executive Officer,  
Unither Pharma

**Roger Jeffs, Ph.D.,**  
President and  
Chief Operating Officer

**Shola Oyewole,**  
Chief Information Officer

**Martine Rothblatt, Ph.D.,**  
Chairman and  
Chief Executive Officer

**Paul Mahon,**  
Senior Vice President and  
General Counsel

**Fred Hadeed,**  
Chief Financial Officer

**Ricardo Balda,**  
Chief Executive Officer,  
Medicomp

**Peter Gonze,**  
Chief Operating Officer,  
Unither Pharmaceuticals

**2002 was the best** year yet in United Therapeutics' six-year history. We achieved our original *raison d'être*, namely FDA approval of a new medicine for primary pulmonary hypertension (PPH). In fact, we did much better than we originally dreamed, for the new medicine, called Remodulin, was approved by the FDA not only for PPH, but also for the much more prevalent disease of pulmonary arterial hypertension (PAH). Indeed, Remodulin has the broadest label of any medicine for the treatment of this life-threatening condition.

As the year rolled on, we added Israeli and Canadian approvals of Remodulin, while bringing in over \$21 million of Remodulin sales in just over six months. By the end of the year, well over 500 patients were being kept alive on Remodulin, representing approximately 20% of our target market of patients on intravenous alternatives to Remodulin.

Soon after United Therapeutics was formed, we began to augment our pulmonary hypertension mission by acquiring the rights to other technologies for chronic, life-threatening conditions. In this way we would leverage the expertise we gained with Remodulin into new therapeutic areas, while heightening the upside potential for our shareholders and reducing the risk inherent in a one-drug business. 2002 was also a great year for this strategy of focused diversity. Our potential medicine for ovarian cancer, OvaRex, commenced its pivotal trials, while a lead glycobiology molecule began clinical testing for hepatitis C. In addition, our arginine and cardiac monitoring businesses achieved near profitable revenue run rates.

United Therapeutics' strategy of focused diversity can be summarized with the following key points:

- One Mission – chronic therapy for life-threatening conditions
- Three Market Segments – cardiovascular, oncology, and infectious diseases

- Five Technology Platforms – prostacyclin analogs, arginine formulations, telemedicine, immunotherapeutic monoclonal antibodies, and glycobiology
- Fifteen Products and Product Candidates – from a recently commercialized product such as Remodulin to an early stage product candidate such as ProstaRex for prostate cancer

This focused diversity strategy enables us to concentrate our staff resources and capital in areas that are our core competencies, such as clinical development of pharmaceuticals for chronic, life-threatening conditions. This strategy also enables us to benefit from intra-corporate synergies. For example, our cardiac monitoring customers can be entry points for our Remodulin and arginine sales efforts, while other Remodulin and arginine prescribers can be introduced to our industry-leading cardiac Holter monitors.

2002 was also a very positive year for United Therapeutics in terms of financial performance. Revenues rose 425%, from \$5.7 million to over \$30 million, while the loss from operations fell by more than 50% to its lowest level since we went public in 1999. We ended the year with virtually no debt and over \$130 million in cash and investments. Indeed, as a hands-on manager, I must share with you my absolute delight over having almost no net outflow of cash during the 4th quarter.

The ability of United Therapeutics to accomplish such an outstanding year is due to the extraordinary efforts of teams headed by our seven-person Executive Committee:

- Roger Jeffs, President and Chief Operating Officer, heads our Clinical Development Group in Research Triangle Park, NC
- David Walsh, Executive Vice President and Chief Operating Officer, Production, heads our Pharmaceutical Production Group in Chicago, IL
- Fred Hadeed, Chief Financial Officer, heads our Corporate and Financial Group in Silver Spring, MD
- Paul Mahon, Senior Vice President and General Counsel, heads our Legal and Governmental Affairs Group in Washington, DC

- Yu-Lun Lin, President and Chief Executive Officer of our Unither Pharma subsidiary, heads our Arginine Group in Satellite Beach, FL
- Ricardo Balda, Chief Executive Officer of our Medicomp subsidiary heads our Telemedicine Group in Melbourne, FL
- Peter Gonze, Chief Operating Officer of our Unither Pharmaceuticals subsidiary, heads our Oncology Group in Wellesley Hills, MA

The efforts of these teams are seamlessly sewn together using state-of-the-art networking technology managed by Shola Oyewole, our Chief Information Officer. Ultimately, we are all working to support our company's various sales and marketing efforts, especially those of our lead product, which are led worldwide by Robert Roscigno, Vice President of Commercial Development, and from our UK office, by Carl Sterritt, Director of European Commercial Development.

While 2002 was a great year for United Therapeutics, as we look toward 2003 we feel that the encore metaphor would not be appropriate. We still have major challenges ahead of us, such as growing Remodulin sales in pulmonary arterial hypertension, successfully completing a Phase IV post-approval study of Remodulin in pulmonary arterial hypertension, further development of Remodulin in new indications such as critical limb ischemia, and proof of safety and efficacy in our oncological and infectious disease programs. Of paramount importance is demonstrating our ability to operate the company profitably. Hence, our goal for 2003 is for the year to be accounted for as having been an even better chapter in an ever-more exciting book.

The robust United Therapeutics pipeline, if successfully developed, has enough compounds and product candidates to push revenues and earnings ever higher for many years to come. It is to the realization of this potential to which all of us at United Therapeutics are steadfastly committed.

Thank you for being great shareholders to work for.

Sincerely,



Martine Rothblatt, Ph.D.  
Chairman and CEO

# What Do We Know About

by Dr. Stuart Rich, Professor of Medicine and Director, Rush Heart  
Institute Center for Pulmonary Heart Disease, Rush Presbyterian  
St. Luke's Hospital, Chicago



# Pulmonary Hypertension

## And How Do We Treat It?

**Introduction** – The causes of pulmonary arterial hypertension include primary pulmonary hypertension, and pulmonary hypertension associated with the collagen vascular diseases, congenital systemic to pulmonary shunts, portal hypertension, HIV infection, anorexigen use, and persistent pulmonary hypertension of the newborn. Afflicted patients share a common histopathology that includes pulmonary vascular abnormalities involving the endothelium, smooth muscle cells, and extracellular matrix. The most common features are medial hypertrophy, eccentric and concentric intimal fibrosis, recanalized thrombi appearing as fibrous webs, and plexiform lesions.

**Pathobiology** – There are likely several pathobiologic processes that result in pulmonary arterial hypertension as a final common pathway. These include inhibition of the voltage regulated potassium channel producing vasoconstriction of the pulmonary artery smooth muscle cells, reduced expression of nitric oxide synthase in the endothelium of the pulmonary arterial bed, increased expression of endothelin and basic fibroblast growth factor, and thrombin deposition related to a procoagulant state. The types of abnormalities that occur are likely influenced by the patient's genotype and exposure to risk factors that serve to trigger these processes.

### **PRIMARY PULMONARY HYPERTENSION**

Primary pulmonary hypertension (PPH) is uncommon, with an estimated incidence of two cases per million. There is a strong female predominance, with most patients presenting in the fourth and fifth decades, although the age range is from infancy to greater than 60 years.

**Genetic considerations** – Familial primary pulmonary hypertension accounts for 12-20% of cases of PPH, and is characterized by autosomal dominant inheritance, variable age of onset, and incomplete penetrance. The clinical and pathologic features of familial and sporadic PPH are identical. Heterozygous germline mutations that involve the gene coding the Type II bone morphogenetic protein receptor (BMPR II), a member of the transforming growth factor beta superfamily, have been found to underlie many cases of familial PPH and has been designated as the PPH I gene located on chromosome 2q31. An interruption in the BMP-mediated signaling pathway will predispose the cells within the small pulmonary arteries to proliferation rather than apoptosis. These observations support the concept that pulmonary arterial hypertension is a result of abnormal proliferation of pulmonary vascular endothelial and smooth muscle cells.

**Natural history** – The natural history of pulmonary arterial hypertension is uncertain because initially the disease can be asymptomatic. Because the predominant symptom is dyspnea, which can have an insidious onset, the disease is typically diagnosed late in its course. Prior to current

therapies, series have reported a mean survival of 2-3 years for patients with primary pulmonary hypertension from the time of diagnosis. It appears that the survival of patients with pulmonary hypertension associated with congenital heart disease is longer, and the survival of patients with associated scleroderma is shorter. Functional class remains a strong predictor of survival, with patients who are Functional Class IV having a mean survival of less than six months. The cause of death is usually right ventricular failure, which is manifested by progressive hypoxemia, tachycardia, hypotension, and edema.

**Diagnosis** – A thorough diagnostic evaluation to look at all potential causes for pulmonary hypertension should be undertaken. The most common symptom attributable to pulmonary hypertension is shortness of breath with effort, which is non-specific. Other common symptoms are fatigue, angina pectoris that may represent right ventricular ischemia, syncope, near syncope, and peripheral edema.

The chest x-ray generally shows enlarged central pulmonary arteries. The lung fields may or may not reveal other pathology. The electrocardiogram usually reveals right axis deviation and right ventricular hypertrophy. The echocardiogram will demonstrate right ventricular enlargement, a reduction in left ventricular cavity size, and a tricuspid regurgitant jet that reflects right ventricular systolic pressure. Pulmonary function tests are helpful to document underlying obstructive airways disease, or severe restrictive lung disease. Hypoxemia and an abnormal diffusing capacity for carbon monoxide are common findings of pulmonary hypertension of most causes. A perfusion lung scan will almost always be abnormal in patients with thromboembolic pulmonary hypertension. However, diffuse patchy filling defects of a non-segmental nature can often be seen in longstanding pulmonary hypertension in the absence of thromboemboli.

Cardiac catheterization is mandatory to accurately measure pulmonary artery pressure and cardiac output, exclude an underlying cardiac shunt, and precisely determine left ventricular filling pressures. Because of the difficulty in obtaining accurate pulmonary capillary wedge pressures in these patients, it is desirable that a left heart catheterization be performed to determine left ventricular end diastolic pressure as the cause of the pulmonary hypertension. It is also recommended that patients with pulmonary arterial hypertension undergo drug testing with a short-acting pulmonary vasodilator at the time of cardiac catheterization to determine the extent of pulmonary vasodilator reactivity (see Figure 1). Inhaled nitric oxide, intravenous adenosine, and intravenous epoprostenol appear to have similar effects in reducing pulmonary artery pressure acutely with little effect on the systemic vascular bed. Maximal physiologic effectiveness of the drug is determined at the highest tolerated dose. Laboratory tests should also be performed, including antinuclear antibody and HIV testing.

On occasion, a patient may have marked elevations in pulmonary artery pressure in association with obstructive or interstitial lung disease, essential hypertension, ischemic heart disease, or valvular heart disease. Although it may appear that the pulmonary hypertension is out of proportion to the underlying associated condition, it likely represents a pulmonary vasoconstrictive response to the associated condition, which is serving as a trigger of the pulmonary arteriopathy. The distinction is important because the treatment of pulmonary hypertension should always include treating the underlying associated cause.

**Treatment** – Because the pulmonary vascular resistance can increase dramatically with exercise, patients should be cautioned against participating in activities that demand increased physical stress. Digoxin may increase cardiac output and lower circulating levels of norepinephrine. Diuretic therapy relieves peripheral edema and may be useful in reducing right ventricular volume overload in the presence of tricuspid regurgitation. Resting and exercise pulse oximetry should be measured, as oxygen supplementation will help alleviate dyspnea and right ventricular ischemia in patients whose arterial oxygen saturation is reduced. Anticoagulant therapy is advocated for all patients on the basis that thrombin deposition occurs in the pulmonary circulation, which can serve as a growth factor to promote the disease process. One retrospective study and one prospective study demonstrated that the anticoagulant warfarin increases survival of patients with primary pulmonary hypertension. The dose of warfarin is generally titrated to achieve an INR of 2.0 - 3.0 of control.

#### **Calcium channel**

**blockers** – Patients who have substantial reductions in pulmonary arterial pressure from short-acting vasodilators at the time of catheterization may be candidates to receive oral calcium channel blockers. Typically, patients will require high doses (e.g., nifedipine 240 mg/day or amlodipine 20 mg/day). Patients who respond favorably will usually have dramatic reductions in pulmonary artery pressure and pulmonary vascular resistance associated with improved symptoms, regression of right ventricular hypertrophy, and improved survival with chronic therapy. Less than 20% of the patients appear to respond to calcium channel blockers in the long term. These drugs can be particularly hazardous when given in patients who are unresponsive, as they can result in hypotension, hypoxemia, tachycardia, and worsening right heart failure.

**Prostacyclins** – Prostacyclin raises cAMP levels in vascular smooth muscle cells and works via vasodilation, growth inhibition, inhibition of platelet aggregation, and cardiac inotropic effects. Epoprostenol (Flolan) is the best characterized approved treatment of pulmonary arterial hypertension for patients who are Functional Class III or IV and unresponsive to other therapies. Clinical trials have demonstrated an improvement in symptoms and exercise tolerance, and a reduction in mortality even if no acute hemodynamic response to drug challenge occurs. Recent reports have documented sustained benefits for more than

ten years in some patients. The drug can only be administered intravenously and requires placement of a permanent central venous catheter and infusion through an ambulatory infusion pump system. It generally takes several months to gradually up titrate the dose to optimal clinical efficacy, which is usually between 25-50 ng/kg/min. Side effects include flushing, jaw pain, and diarrhea, which are generally tolerated by most patients. The major problem with this therapy has been infection related to the venous catheter, which requires close monitoring and diligence on behalf of the patient.

Recently, treprostinil (Remodulin) has been approved for patients with pulmonary arterial hypertension who are Functional Class II-IV to diminish symptoms associated with exercise. An analog of epoprostenol, treprostinil has a longer half-life and is stable at room temperature, allowing for it to be administered subcutaneously through a small infusion pump that was originally developed for insulin. Clinical trials have demonstrated an increase in exercise capacity using a six-minute walk test and a reduction of symptoms of dyspnea. The major side effect with this treatment has been local pain at the infusion site. Patients who are stable on intravenous epoprostenol can be transitioned to subcutaneous treprostinil, eliminating the need for a chronic indwelling intravenous catheter.



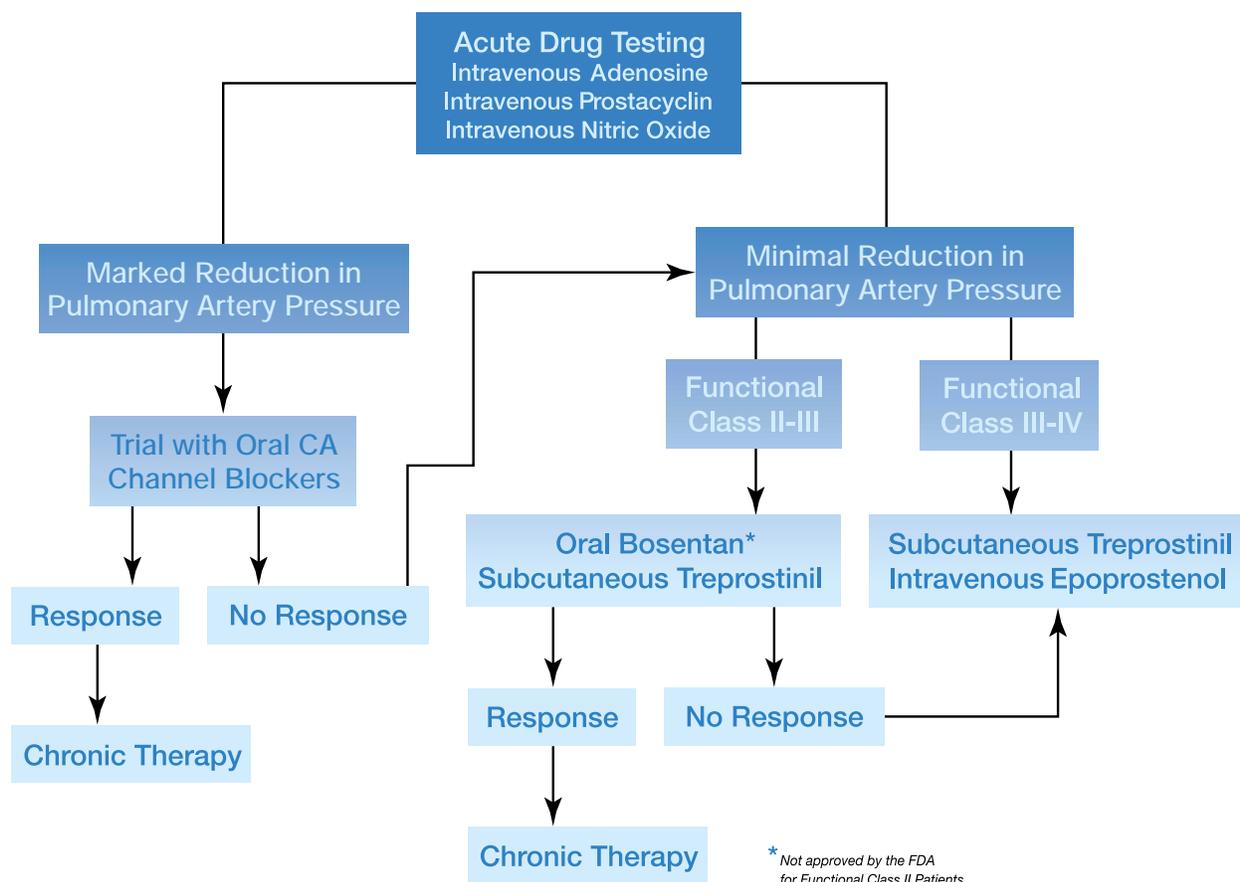
*Remodulin (treprostinil sodium) Injection is approved as a continuous subcutaneous infusion for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise.*

#### **Endothelin receptor antagonists**

– Endothelin levels are increased in pulmonary hypertension and cause vasoconstriction and smooth muscle cell proliferation. The non-selective endothelin receptor antagonist bosentan (Tracleer) was recently approved as an oral treatment of pulmonary arterial

hypertension for patients who are Functional Class III and IV to diminish symptoms associated with exercise. In randomized clinical trials, bosentan was shown to improve exercise tolerance as measured by an increase in six-minute walk distance, improve functional class, and extend time until clinical worsening versus placebo. Therapy is initiated at a low dose (62.5 mg BID) for the first month and then increased to 125 mg BID thereafter. Because of the high frequency of abnormal hepatic function tests associated with drug use, primarily an increase in transaminases, it is recommended that patients have liver function tests monitored monthly throughout the duration of use. Bosentan is also contraindicated in patients who are currently on cyclosporine A or glyburide. There are no data to support the use of bosentan for some forms of pulmonary hypertension.

**Sildenafil** – There have been several case reports on the use of sildenafil (Viagra), an oral phosphodiesterase-5 inhibitor, as a treatment of pulmonary hypertension. Phosphodiesterase 5 is responsible for the hydrolysis of cGMP in the lung, the mediator through which nitric oxide lowers pulmonary artery pressure and inhibits pulmonary vascular growth. These reports suggest that oral sildenafil has a similar efficacy to inhaled nitric oxide. Large randomized clinical trials using sildenafil as a treatment of pulmonary hypertension are being proposed.



**Figure 1:** An algorithm for the selection of optimal drug treatment of a patient with pulmonary arterial hypertension. Although treprostinil is approved for Functional Class IV patients, most experts would initiate therapy with intravenous epoprostenol and consider transitioning to treprostinil once the patient has stabilized, or in circumstances where epoprostenol therapy results in intolerable side effects or recurrent catheter infections.

**Transplantation** – Because of the dramatic effects that intravenous epoprostenol has in stabilizing and improving the clinical course of patients with advanced disease, transplantation is considered for patients who, while on epoprostenol, continue to manifest right heart failure. Acceptable results have been achieved with heart-lung,

bilateral lung, and single lung transplant. The availability of donor organs often influences the choice of procedure. The re-occurrence of primary pulmonary hypertension has never been reported in a patient who has undergone lung transplantation.



"These patients share a common histopathology that includes pulmonary vascular abnormalities involving the endothelium, smooth muscle cells, and extracellular matrix."



"Patients who are stable on intravenous epoprostenol can be transitioned to subcutaneous treprostinil, eliminating the need for a chronic indwelling intravenous catheter."



"An analog of epoprostenol, treprostinil has a longer half-life and is stable at room temperature, allowing for it to be administered through a small infusion pump."

# What Do We Know About

by John P. Cooke M.D. Ph.D., Associate Professor and Director,  
Program in Vascular Medicine and Biology, Stanford University



# Critical Limb Ischemia

## And How Do We Treat It?

**Introduction** – Atherosclerosis is the major cause of death in the United States and Europe, and will soon become the major cause of death and disability in Asia. When atherosclerosis causes narrowing of the coronary arteries, the individual may have angina or a heart attack; when atherosclerosis affects the carotid arteries that supply the brain with blood, a stroke may ensue. Atherosclerosis may also obstruct the leg arteries, a condition known as peripheral arterial disease (PAD). PAD is much more common than is recognized by laypersons or physicians, afflicting about 25% of people over the age of 70 and about 25% of smokers or diabetics over the age of 55. Indeed, about 10 million people in the United States have PAD. In its earliest stages, it is silent. As the blockages in the leg arteries progress, the individual may notice fatigue or cramping in the calf, thigh, or buttocks with walking, a discomfort that is relieved by standing still for a few moments before walking on.

As the obstructions in the leg arteries become more severe, the leg discomfort may occur with very little exertion. The individual becomes very limited, and walking a city block becomes a painful and tedious process. With more progression, pain may occur at rest, typically at night, and almost always in the foot. Relief is obtained by sitting up and dangling the foot over the bed. The blood flow is now so poor that the limb is in jeopardy of developing ulceration and gangrene. At this point, the disease has advanced to the stage of critical limb ischemia (CLI). About 750,000 people in the US have critical limb ischemia. Unfortunately many of these individuals will end up with amputations. Indeed, CLI results in about 200,000 amputations annually in this country.

**Other diseases that can cause CLI** – Atherosclerosis is the most common cause of severe vascular obstructions. However, there are some other diseases that can narrow the leg vessels. Buerger's disease commonly affects young men that are heavy smokers. This disease causes a severe inflammation of the blood vessels in the toes and fingers, associated with blood clots that obstruct the vessels. In severe cases, individuals may lose digits or even the limb. Another cause of CLI is embolization (i.e., clot that has been ejected from a failing heart, or from an aneurysm in the aorta, into the leg). Embolization can cause a dramatic and severe reduction in blood flow to the limb that is manifested by a severely painful, cold, and pale foot.

**Making the Diagnosis of CLI** – Often the individuals are diabetic or smokers. They may have had poorly controlled hypertension and/or high levels of cholesterol for many years. Typically they will have had a gradual progression of symptoms over the years: increasing severity of exertional

leg pain, then foot pain occurring at night, then ulceration of a heel or gangrene of a toe. Often they will have had multiple vascular surgeries or angioplasties in an attempt to relieve the symptoms.

On examination of the leg, the skin appears shiny and hairless. These changes are due to the poor skin blood flow, which causes hair loss, and thinning of the skin. There may be an ulcer on the foot, typically in a weight-bearing part of the foot, (e.g., the heel), or in a part of the foot that is exposed to pressure by poorly fitting shoes. The ulcer is typically round, well-demarcated, painful, and covered with a thick black scab. With the person supine, and the leg raised in the air, the foot becomes very pale, due to poor blood flow. With the person sitting and dangling the leg, the foot becomes very red, because the small blood vessels in the foot are maximally dilated all the time, in a desperate attempt to recruit more blood flow to the foot (thus blood tends to pool in these small vessels, causing the reddish appearance). In a healthy individual, a strong pulse can be felt in the foot, much as one can palpate a pulse in the wrist. But in the individual with CLI, pulses are no longer palpable in the foot. In some cases, the onset of CLI can be rapid. This may be due to embolization as mentioned above. Or it can be due to a sudden worsening of an obstruction, due to clot forming rapidly over a pre-existing narrowing. In these cases, the pace of diagnosis and treatment must be quickened, and a more interventional approach is generally followed. Therefore, the management of these cases (see Figure 2) must be individualized.

**Laboratory studies to assist in the diagnosis** – There are a number of vascular studies that can help to refine the diagnosis of CLI. There are physiological studies that can detect the strength of the pulse (e.g., photoplethysmography), measure the blood pressure at various levels in the leg (Doppler-derived segmental pressure measurements), measure limb blood flow (strain gauge plethysmography or magnetic resonance imaging), and image the blood vessels non-invasively (e.g., with Duplex ultrasound, which can image the vessel by sonography, and can provide information on the velocity of blood flow). However, when the clinical picture is clear, these intermediate steps are generally bypassed and the patient is sent for an angiogram, in preparation for interventional procedures.

**Interventional procedures for CLI** – Typically an individual who has symptoms consistent with a diagnosis of CLI needs an angiogram, with a view toward getting more specific information about where the blockages are so that an interventional procedure can be performed. Interventional procedures include thrombolysis (dissolving clot with medication infused into the leg artery), thrombectomy

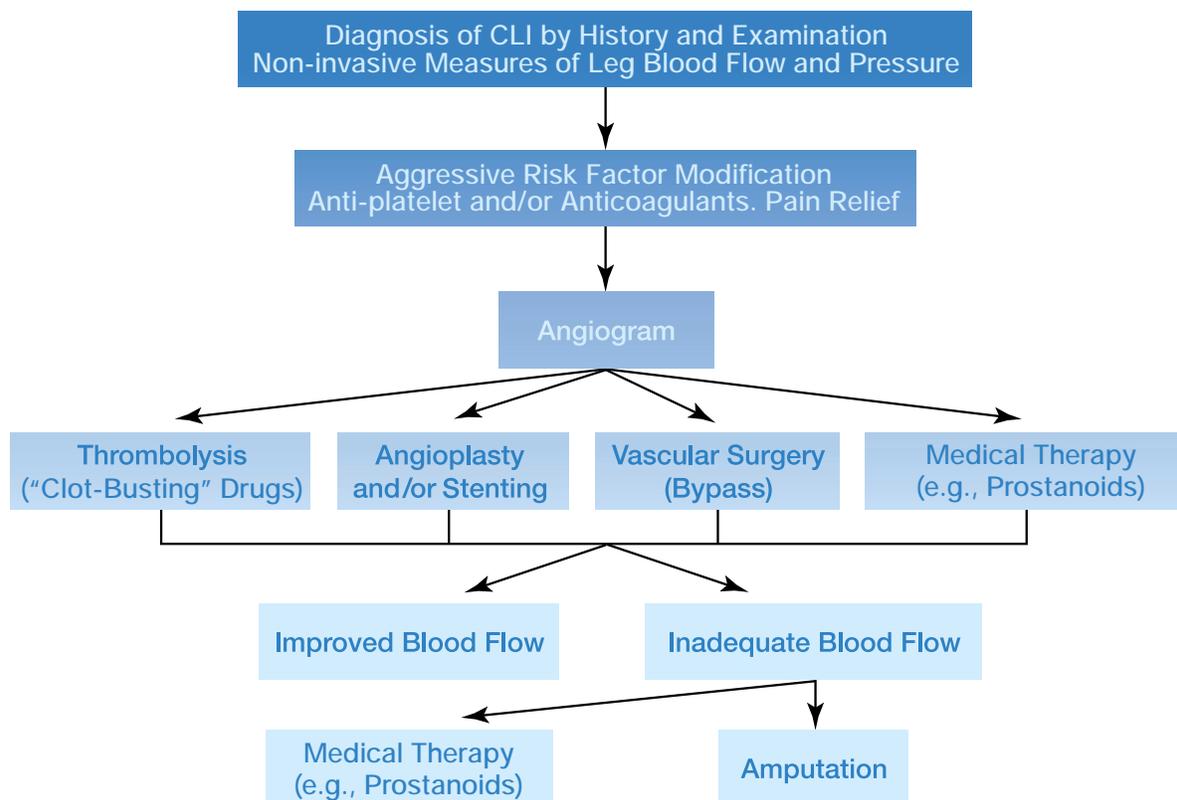


Figure 2: Algorithm for Management of Critical Limb Ischemia.

(extraction of a clot from the leg artery using a balloon catheter), angioplasty (using a balloon catheter to expand the vessel), stenting (using a catheter to place a metal coil inside the artery, so as to expand it), and surgery (using a segment of vein, or a synthetic conduit, to surgically bypass the obstruction, allowing blood to flow around the obstruction and into the native vessel below the obstruction).

Before any of these procedures can be performed, it is necessary to know where the obstructions are. In an individual with CLI, there are often multiple obstructions in the leg artery. Typically, the catheter is placed in the femoral artery (in the groin region) in the opposite leg. The catheter is pushed up the femoral artery, through the iliac artery, and into the aorta, and then is directed downward into the iliac artery of the affected leg. Contrast agent is administered, and x-rays are taken. The contrast agent (a radio-opaque iodinated dye that can be seen on the x-ray) flows through the iliac artery and into the affected leg, outlining the obstructions. Once this is done, it may be possible to use the catheter to perform angioplasty and/or stenting of the plaque that is obstructing the vessel. If the problem is a large blood clot, then clot-busting medicine can be infused through the catheter into the leg artery. If the obstructions are severe or multiple, it may be better to send the individual to the surgeon for a bypass.

### MEDICAL APPROACHES

**Overview** – Unfortunately, about 30% of these procedures fail within a year in these patients. Another 25% of patients are inoperable due to severe and diffuse disease. And even in the patients where the procedure has been successful, 40% have died within four years, usually due to stroke or heart attack. To improve on these figures, we need to use the medical therapy that we have more

effectively, and we also need to develop new medical approaches.

Current medical therapy for the patient with critical limb ischemia involves aggressive risk factor modification to improve longevity; antiplatelet therapy or anticoagulation to prevent clot from forming and causing rapid deterioration; aggressive treatment of any infection; narcotics for severe foot pain; and foot care, with proper foot wear. The latter seems obvious for someone with poor blood flow to the foot, but these are simple measures that are woefully overlooked. About 75% of amputations in diabetics are due to avoidable trauma to the foot (as with poorly fitting shoes). The skin should be well hydrated by an emollient cream, which will make it more supple and less likely to fissure (cracks in the skin which represent portals of entry for infectious agents). Aggressive risk factor modification saves more lives than any surgical or catheter-based intervention. Patients with critical limb ischemia need to be treated intensively with medications (preferably statins) to reduce their LDL cholesterol; anti-hypertensive agents to control their blood pressure; insulin, insulin-releasing, or insulin-sensitizing drugs to lower the blood sugar to normal levels; and agents to thin the blood (i.e., aspirin) or the newer and more effective anti-platelet agent, clopidogrel. Furthermore, it is critical to get these individuals to stop smoking. A successful stop-smoking program includes behavioral therapy (e.g., group counseling sessions), nicotine patches, gums or sprays, and other agents to reduce cravings such as Zyban or clonidine. In addition, proper nutrition is paramount; a modified Mediterranean diet has been shown to improve blood vessel function and to reduce death from cardiovascular disease. These medical and nutritional interventions are targeted to reduce the probability that the patient with CLI will succumb to a heart attack or stroke.

There is also some evidence that the progression of disease in the leg arteries can be slowed by aggressive treatment of high levels of cholesterol. In addition to these therapies, there are some exciting new medical approaches that are showing some promise.

**Intermittent pneumatic compression** – When anecdotal reports began to emerge of ulcer healing and pain relief with the use of intermittent pneumatic compression, they were met with skepticism. Subsequently, small but rigorous clinical trials, including one at the Mayo Clinic, have supported the use of this interesting device. The device consists of a rigid boot that is intermittently pressurized with air. The increase in pressure is timed to the beat of the heart, such that the increase in pressure occurs in diastole, when the heart is resting. The mechanisms by which this device improves the condition of the leg may include maintaining a higher blood pressure in the leg during diastole, at a time when the heart is resting and the blood pressure is dropping; increasing the flow of venous blood back from the leg to the heart, which can improve cardiac output, and can increase the pressure gradient across the leg circulation; and increasing shear stress in the leg vessels, thereby increasing the release from the vessel of nitric oxide and prostacyclin (see below). Whatever the mechanism, ulcer healing and pain relief can be observed after a series of treatments over a period of weeks.

**Prostanoids** – Prostaglandin derivatives have received considerable interest due to a growing body of evidence that suggests that these agents accelerate ulcer healing, circumvent the need for amputation, and reduce pain as well as mortality in patients with critical limb ischemia. (Loosemore, 1994; European Working Group, 1991). In addition, prostanoid therapy is recommended in patients who have a viable limb in which revascularization procedures are impossible, carry a poor chance of success or have previously failed, and particularly in those cases when the alternative is amputation. (TransAtlantic Inter-Society, 2000)

During the past two decades, over 2,000 patients with critical limb ischemia have been studied in European trials involving intravenously administered prostacyclin analogues. (Loosemore, 1994; European Working Group, 1991; Mohler, 2000). Improved ulcer healing and relief of rest pain have been documented.

While promising effects have been observed with intravenous prostanoids, the clinical usefulness of these agents is limited by the fact that an indwelling intravenous line must be used, making the therapy somewhat cumbersome and increasing the risk of infection. If the therapy could be delivered subcutaneously, this would be safer and more convenient than intravenous administration. Recently, the U.S. Food and Drug Administration approved a subcutaneous formulation of treprostinil sodium (Remodulin, United Therapeutics Corporation, Research Triangle Park, NC) for the treatment of patients with pulmonary arterial hypertension. In clinical trials of patients with pulmonary arterial hypertension, treprostinil, administered

subcutaneously, produced significant improvement as compared to placebo in a number of hemodynamic measures, including cardiac index (a measure of pump function of the heart), and pulmonary pressures. A recently published study by Mohler, and colleagues indicated that intravenous treprostinil can also improve blood flow in the legs of patients with severe vascular disease (Mohler, 2000). Unlike previous studies evaluating the vasodilatory effects of prostacyclin analogs, this study used state-of-the-art non-invasive ultrasonography to test the hemodynamic effects of treprostinil. Blood flow in the leg arteries increased 29% during the infusion. In two of four patients in whom blood flow was undetectable prior to the infusion, arterial blood flow at the ankle level was detectable during the infusion of the drug. The treatment was well-tolerated and no serious treatment-related adverse events occurred during the therapy. This positive result, combined with the positive experience in Europe with prostanoid therapy, has been the stimulus for a formal trial of the therapy to gain approval for treating this condition.

**Angiogenesis** – This is an experimental approach not yet proven to be effective, but with exciting animal data, and some preliminary human trials, that suggest proof of concept. Angiogenesis is the creation of "biological bypasses," small vessels that can grow around a blocked artery and thereby provide blood flow to the tissue downstream. Our bodies have the innate capacity to generate biological bypasses, and to some extent this occurs in everyone that has a blocked vessel. In some people, the biological bypass formation is so effective they may never realize that one of their major leg arteries has become blocked over time. However, in most people, the generation of biological bypasses is insufficient. The use of growth factors such as VEGF (vascular endothelial growth factor) and FGF (fibroblast growth factor) are under investigation. However, evidence from our laboratory and others suggests that these agents work in part by increasing the release of prostacyclin and nitric oxide from the vessels, substances which play a critical role in vessel growth. Prostacyclin and nitric oxide have each been shown to enhance the growth of endothelial cells that line the blood vessels. It is the growth of endothelial cells, and their organization into tubules, that is one of the first steps in angiogenesis.

Nitric oxide (NO) and prostacyclin are normally produced in sufficient quantities in the healthy blood vessel to maintain blood flow at normal levels and to prevent obstructions from forming. In diseased vessels, the production of these vasoprotective molecules is markedly reduced. As described above, administration of prostanoids can replace the loss of endogenous prostacyclin. Ultimately, it may be that combinations of growth factors with prostacyclin and/or NO-enhancing agents (such as L-arginine) may be required to maximally improve blood flow to the severely diseased leg circulation.

# Multiple Market Segments

## Telemedicine

Cardiac monitors are small portable devices taken home by patients to check for irregular heart rhythms over a period of days or weeks. United Therapeutics offers doctors the smallest such monitors in the industry equipped with a software algorithm that can recognize 39 different kinds of arrhythmias. Ultimately this technology could be used by millions of healthy people as a consumer-driven desire to monitor their hearts' performance on an ongoing basis.



## OvaRex

Pivotal trials are underway of OvaRex for prevention of the recurrence of ovarian cancer after initial therapy. If this medicine proves to be successful, it will pave the way for similar therapies at an earlier stage of development. United Therapeutics owns the rights to similar potential therapies for the treatment of prostate, breast, lung, pancreatic, colorectal and multiple myeloma cancers.



## HeartBar®

The HeartBar is a 6-gram formulation of arginine, an essential amino acid patented by Stanford University (and exclusively licensed to United Therapeutics) for the promotion of vascular function. HeartBar is a convenient source of supplemental arginine\* required by the body to produce nitric oxide, which is critical for maintaining circulatory function. Multi-gram arginine supplementation increases vasodilation.



\* Arginine is an essential part of a healthy diet. People with sufficient arginine in their diet may not require arginine supplementation and HeartBar is not intended to diagnose, treat, cure, or prevent any disease.



Sir John Vane, D.Sc. F.R.S.



Robyn J. Barst, M.D.



Professor  
Baruch S. Blumberg, Ph.D.



Professor  
Raymond A. Dwek, F.R.S.

# Scientific Advisory Board

We are proud of our Scientific Advisory Board. It is chaired by Sir John Vane, D.Sc., F.R.S. a Nobel Laureate who co-discovered the molecule prostacyclin, upon which much of our business is based. His knowledge is of immense value to us as we explore the use of prostacyclin-like molecules (such as Remodulin) in cardiovascular conditions. The Scientific Advisory Board member who helps us pilot the use of variants of the prostacyclin molecule in the field of pulmonary hypertension is a globally recognized expert in this condition, clinician-scientist Robyn J. Barst, M.D.

As we extended our business into infectious diseases, we strengthened our Board with Nobel Laureate Baruch S. Blumberg, Ph.D., who discovered the hepatitis B virus and created the hepatitis B vaccine, an innovation that has saved millions of lives. Professor Blumberg works closely with another of our Board members, Raymond A. Dwek, F.R.S., who discovered our iminosugar-based anti-infective platform of molecules (such as our lead drug candidate for treating hepatitis C, UT-231B). Professor Dwek is also able to share with us some of the brilliance that permeates University of Oxford's Biochemistry Department, which he chairs, and its Glycobiology Institute, which he founded. The anti-infectives expertise of Professors Blumberg and Dwek is further complemented on our Scientific Advisory Board by Urban Ramstedt, Ph.D., Head of Immunology at Zycos Inc., and an expert on retroviruses, particularly HIV and hepatitis C.

It is also important to have individuals on a Scientific Advisory Board who have operational responsibility and vast expertise overseeing the appropriateness of how scientific breakthroughs are translated into clinical protocols, and how medical discoveries are integrated into clinical practice. For us, we are honored to have as these individuals Sir Magdi Yacoub, M.D., F.A.C.S., one of the world's foremost transplant surgeons and cardiopulmonary scientists, Victor J. Dzau, M.D., Chairman of Medicine at Harvard University's Brigham & Women's Hospital, and the Hon. Louis W. Sullivan, M.D., founding President and now President Emeritus of Morehouse School of Medicine and former Secretary of the United States Department of Health and Human Services.

The Scientific Advisory Board at United Therapeutics plays an important role. Fortunately for us, the caliber of the scientists on our Board are second to none in our missions of developing prostacyclin-like molecules and arginine supplementation for cardiovascular medicine and proving the usefulness of iminosugar compounds for safely treating serious infectious disease.

Professor  
Victor J. Dzau, M.D.

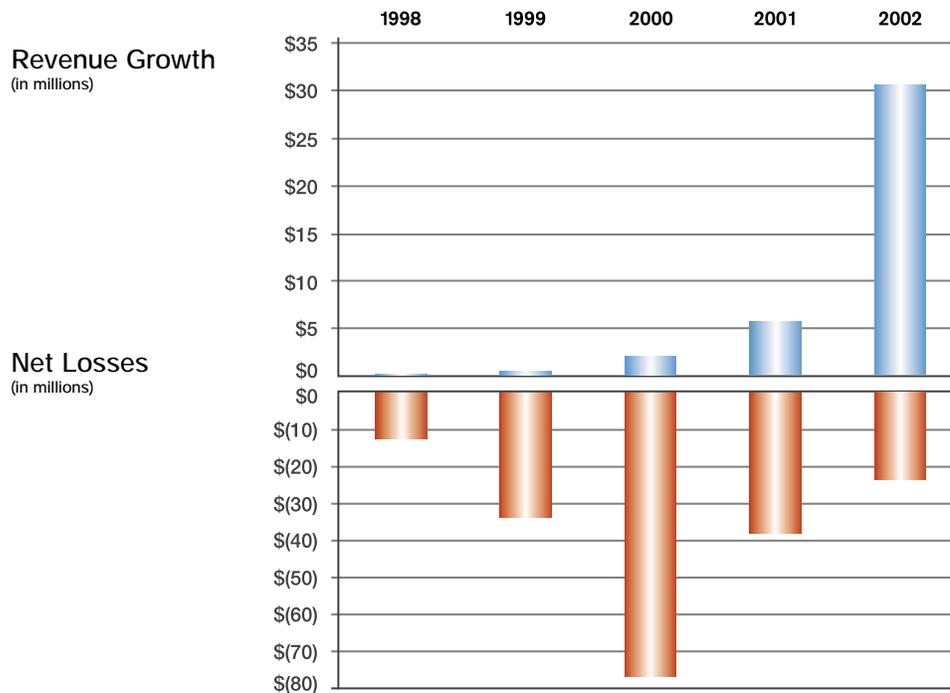
Urban Ramstedt, Ph.D.

Louis W. Sullivan, M.D.

Professor Sir Magdi  
Yacoub, M.D., F.A.C.S.

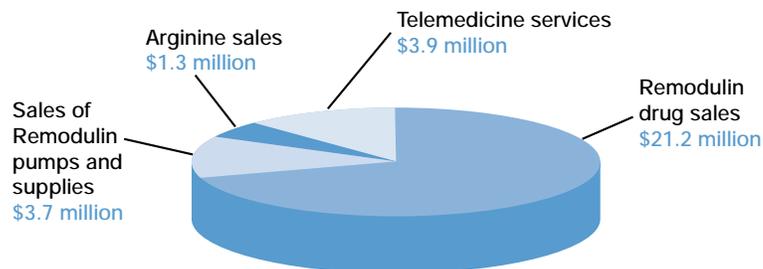


# Selected Financial Highlights



**Revenues** – United Therapeutics revenues grew to over \$30 million in 2002. This 425% growth from the prior year was fueled by demand for Remodulin which was launched in May 2002 in the United States. Demand for United Therapeutics' other products grew in 2002 as well. Consequently, annual net losses have fallen significantly from their highest level in 2000.

**2002 Revenue Sources**  
Total \$30.1 million



**Cash and Investments** – United Therapeutics had cash, cash equivalents, and investments totaling approximately \$132.7 million at December 31, 2002.

# Company Summary

United Therapeutics is a biotechnology company focused on developing chronic therapies for life-threatening conditions in three therapeutic areas: cardiovascular, oncology, and infectious diseases. In these segments, United Therapeutics is actively developing five technology platforms: prostacyclin analogs, immunotherapeutic monoclonal antibodies, glycobiology, arginine formulations, and telemedicine.

At United Therapeutics, we find tremendous inspiration for our work and view our products as being new beginnings for patients and doctors, with quality of life as our utmost therapeutic goal. The theme of United Therapeutics is "Medicines for Life" because all of our therapeutics address life-threatening illnesses.

Much of United Therapeutics' resources are focused on cardiovascular health, including developing analogs of the endogenous hormone prostacyclin for the treatment of pulmonary arterial hypertension and critical limb ischemia, telemedicine services for patients with an array of possible cardiac arrhythmias, and arginine supplementation therapy. United Therapeutics' second principal focus is oncology, and the company is undertaking the largest ever pivotal trial of a potential medicine for preventing the recurrence of ovarian cancer. This medicine is part of a family of similar immunotherapeutic monoclonal antibody therapies licensed to United Therapeutics which are designed to combat prostate, breast, lung, pancreatic, colorectal, and multiple myeloma cancers. United Therapeutics' third focus is in the field of infectious disease, where the company is targeting hepatitis C and other diseases with unique glycobiology compounds. While this work is at an early stage, it holds immense promise. The diseases being targeted afflict over a billion people worldwide, and the compounds are part of an entire new class of pharmacological agents.

The company's mission is carried out using corporate partners for product sales and academic centers for research whenever feasible, complemented by in-house commercialization professionals and our commitment to providing doctors and patients with accurate information and ongoing research related to our products. This strategy streamlines company overhead and enables company employees to concentrate on clinical trials, regulatory approvals and business development. United Therapeutics generally retains all rights to the products it develops.



Raymond Dwek, F.R.S., Professor of Glycobiology, Director of the Glycobiology Institute, and Chairman of the Department of Biochemistry at University of Oxford, holds a model of a sugar molecule related to United Therapeutics' glycobiology program. Professor Dwek is a member of both the United Therapeutics Board of Directors and Scientific Advisory Board.

# Corporate Information

## Management

Ricardo Balda  
Chief Executive Officer  
Medicomp, Inc.

Peter C. Gonze  
Chief Operating Officer  
Unither Pharmaceuticals, Inc.

Fred T. Hadeed  
Chief Financial Officer

Roger Jeffs, Ph.D.  
President and Chief Operating Officer

Yu-Lun Lin  
President and Chief Executive Officer  
Unither Pharma, Inc.

Paul A. Mahon, J.D.  
Senior Vice President and General Counsel

Shola Oyewole, MSc., M.C.S.E.+1  
Chief Information Officer

Martine Rothblatt, Ph.D., J.D., M.B.A.  
Chairman and Chief Executive Officer

David Walsh, Ph.D.  
Executive Vice President and  
Chief Operating Officer, Production

## Board of Directors

Ricardo Balda\*

Professor Raymond A. Dwek, F.R.S.  
Professor of Glycobiology  
Director of the Glycobiology Institute  
Chairman of the Department of  
Biochemistry  
University of Oxford

R. Paul Gray  
Founding member, Core Concepts, LLC  
Chief Financial Officer and Director,  
Surgical Safety Products, Inc.

Henry Beecher Hicks, III, M.B.A.  
Principal  
Equilibrium Growth Advisors, LLC

Roger Jeffs, Ph.D.\*

Raymond Kurzweil  
Founder, Chairman, and  
Chief Executive Officer  
Medical Learning Company, Inc.

Michael C. Miles, M.B.A.  
Co-founder  
McManus & Miles

Christopher Patuskus, J.D., M.G.A.  
Deputy Director, Chief Operating Officer,  
and Member of the Faculty  
Fels Institute of Government  
University of Pennsylvania

Martine Rothblatt, Ph.D., J.D., M.B.A.\*

Hon. Louis W. Sullivan, M.D.  
Founding President and President Emeritus  
of Morehouse School of Medicine  
Former Secretary of United States  
Department of Health and Human Services

## Scientific Advisory Board United Therapeutics

Sir John Vane, D.Sc., F.R.S.  
1982 Nobel Laureate in Physiology  
or Medicine  
Chairman of the United Therapeutics  
Scientific Advisory Board

Robyn Barst, M.D.  
Columbia University, New York  
Professor of Pediatrics, Columbia University  
College of Physicians & Surgeons  
Director, Pulmonary Hypertension Center,  
New York Presbyterian Hospital

Professor Baruch S. Blumberg, Ph.D.  
1976 Nobel Laureate in Physiology  
or Medicine  
Fox Chase Distinguished Scientist,  
Fox Chase Cancer Center

Professor Raymond A. Dwek, F.R.S.  
Professor of Glycobiology  
Director, of the Glycobiology Institute  
Chairman of the Department of  
Biochemistry  
University of Oxford

Professor Victor J. Dzau, M.D.  
Chairman, Department of Medicine  
Brigham & Women's Hospital  
Harvard Medical School

Urban Ramstedt, Ph.D.  
Head of Immunology  
Zycos, Inc.  
Lexington, Massachusetts

Hon. Louis W. Sullivan, M.D.  
Founding President and President Emeritus  
of Morehouse School of Medicine  
Former Secretary of United States  
Department of Health and Human Services

Professor Sir Magdi Yacoub, M.D., F.A.C.S.  
England's National Heart and Lung Institute

## Investor and Shareholder Relations

Andrew Fisher, J.D.  
Deputy General Counsel and Vice  
President, Investor Relations

Therese Fergo, M.B.A.  
Staff Vice President, Employee and  
Shareholder Relations

## Transfer Agent and Registrar

The Bank of New York  
Shareholder Relations Department  
P.O. Box 11258  
Church Street Station  
New York, New York 10286  
(800) 524-4458  
e-mail: [shareowners@bankofny.com](mailto:shareowners@bankofny.com)  
Stock Transfer Website: [www.stockbny.com](http://www.stockbny.com)

## Attorneys

Akin Gump Strauss Hauser & Feld, LLP  
Robert S. Strauss Building  
1333 New Hampshire Avenue, N.W.  
Washington, D.C. 20036  
Tel. (202) 887-4000  
Fax. (202) 887-4288

## Auditors

KPMG LLP  
1660 International Drive  
McLean, Virginia 22102  
Tel. (703) 747-6000  
Fax. (703) 747-7600

## Corporate Headquarters

1110 Spring Street  
Silver Spring, Maryland 20910  
Tel. (301) 608-9292  
Fax. (301) 608-9291

## Research and Development

One Park Drive  
P.O. Box 14186  
Research Triangle Park,  
North Carolina 27709  
Tel. (919) 485-8350  
Fax. (919) 485-8352

## Manufacturing

2225 W. Harrison Street  
Chicago, Illinois 60612  
Tel. (312) 421-1819  
Fax. (312) 421-8177

## Legal and Governmental Affairs

1735 Connecticut Avenue, N.W.  
Washington, D.C. 20009  
Tel. (202) 483-7000  
Fax. (202) 483-4005

## Subsidiaries

Medicomp, Inc.  
7845 Ellis Road  
Melbourne, Florida 32904  
Tel. (321) 676-0010  
Fax. (321) 676-2282  
[www.medicompinc.com](http://www.medicompinc.com)

Unither Pharma, Inc.  
1077 Highway A1A  
Satellite Beach, Florida 32937  
Tel. (321) 779-1441  
Fax. (321) 779-1645  
[www.unitherpharma.com](http://www.unitherpharma.com)

Unither Pharmaceuticals, Inc.  
15 Walnut Street  
Wellesley Hills, Massachusetts 02481  
Tel. (781) 235-7412  
Fax. (781) 235-7241

## Common Stock

Listed on Nasdaq National  
Market symbol "UTHR"

## Annual Meeting

July 9, 2003

## Internet Access

[www.unither.com](http://www.unither.com)

\* Unither Therapeutics' Management



Medicines for Life®

**Corporate Headquarters**  
1110 Spring Street  
Silver Spring, Maryland 20910  
Tel. (301) 608-9292  
Fax. (301) 608-9291

[www.unither.com](http://www.unither.com)