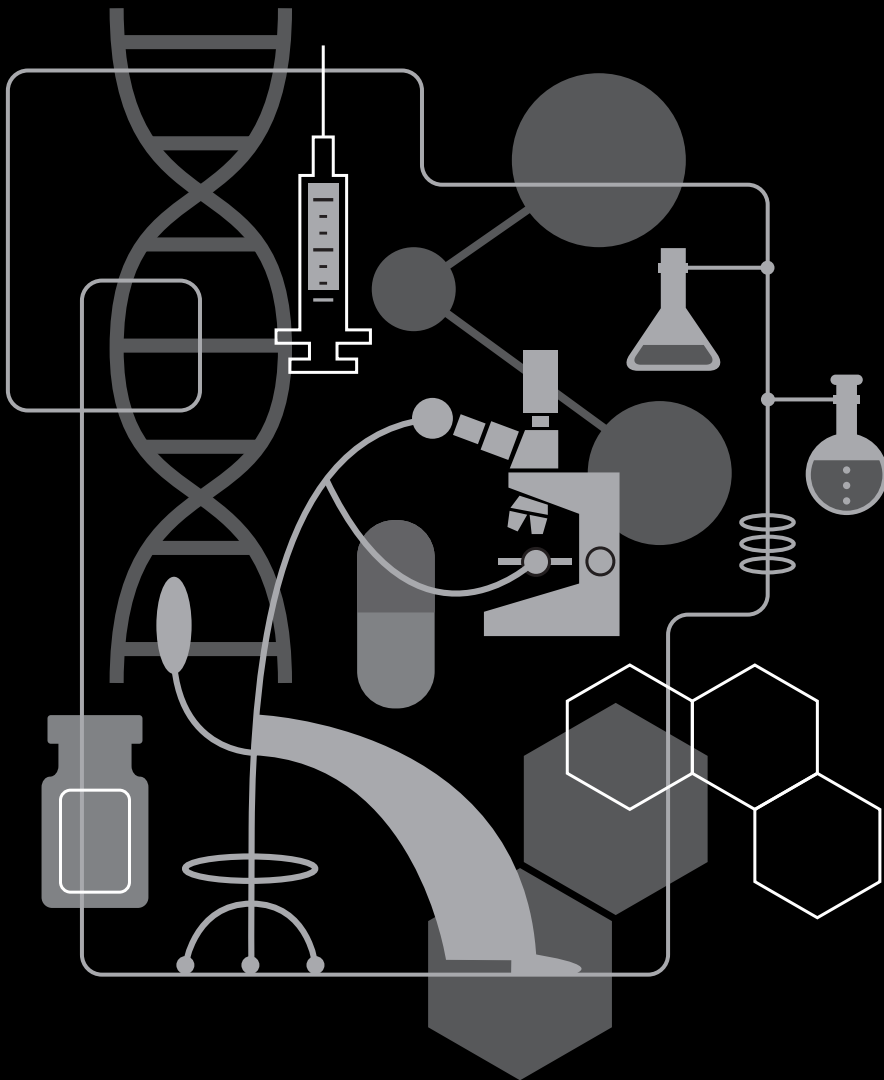


“Vices enter into the composition of virtues as poisons into the composition of certain medicines. Prudence and common sense mix them together, and make excellent use of them against the misfortunes that attend human life.”

François, Duc De La Rochefoucauld





## New Medicines, New Hope

A LOOK AT MARYLAND'S THERAPEUTIC COMPANIES



Therapeutics companies are the indisputable stars of the bioscience industry. When things are good, they are the darlings of Wall Street and the press. Capital-intensive and full of promise, they are the companies that bring forth life-altering new treatments for patients with debilitating disease, and substantial returns for their founders and investors. However, building a sustainable therapeutics company and seeing it through to a successful exit via acquisition or IPO is a daunting challenge. This chapter reveals some of what it takes to meet that challenge, and uncovers some of the “best practices” employed by the Maryland companies and personalities that are making it happen.

### Sequoia Pharmaceuticals

Sequoia Pharmaceuticals was founded late in 2001, in the living room of Chief Science Officer John Erickson's home. The founders, a group that included six scientists and one businessman, were developing a plan that they hoped would translate good science into good business. So far their plan is working. Not only has the company successfully raised \$22 million in venture capital, they've laid plans to send their first drug into clinical trials later this year.

Like most startup biotechs, Sequoia is a company driven by science. According to Chief Operating Officer Gary Altman, “The company was founded to design drugs that combat some of the world's most difficult diseases, with a focus on retro viruses. And that remains our focus.”

But unlike so many startup pharmaceutical companies, most of which fail, Sequoia has succeeded by weaving a passion for science into every strategic business decision the company has made. This philosophy was demonstrated early in the company's history by the decision to include Altman among the company's co-founders. Although Altman does have a background in biochemistry, he has spent almost his entire career in private industry, building and running successful businesses. “I think that my having some science background is helpful in that it is easy for me to interact with the other scientists—from their point of view it adds credibility,” Altman said.

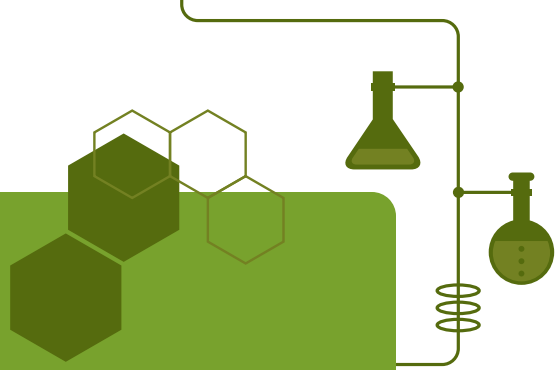
Altman believes that too often well-intentioned scientists embark on projects without realizing the importance of incorporating business acumen into a technical start-up. He believes that many of the top-tier venture capitalists look for business expertise as well as technical expertise when evaluating investment opportunities. Lack of proper business strategy “is probably responsible for the high failure rate of biotech startups,” Altman said. “And it's not that the ideas are not good.” It's that too often, scientists embark on projects with such tremendous enthusiasm and confidence that they just expect that their technology will be readily accepted and that

funding will come. “They mistakenly believe that anyone bright enough to understand the technology will buy into the technology,” he said. And although this may happen occasionally, it is certainly not the norm.

In the case of Sequoia, the company was started with the founder's personal funds, an angel investor, and an eye toward a plan to avoid venture capital. “We had heard stories of unpleasant interactions, and we were confident that the VCs would eventually have control of the company and that their goals might not overlap with our goals,” Altman said. As the initial funds the founders pooled to start the company eventually ran out, Sequoia executives explored numerous strategies to conserve cash. “We made several attempts at budgets,” Altman recalls. “We probably had hundreds of budgets; none of them were correct, but we got better at doing it.” Eventually, company executives set out to raise capital and explored a number of strategies, including a non-profit model—one that relied exclusively on grant funding and philanthropy. Although they were able to secure a small amount of angel capital, the founders soon realized that Sequoia's burn rate was not sustainable without venture backing.

The problem, the company soon discovered, was that acquiring venture capital wasn't as simple as just asking for it. A typical VC firm receives more than 300 proposals a month and funds, on average, fewer than 10 per year. After six months of unsuccessfully pitching to venture capital firms in the second half of 2003, Sequoia executives halted their efforts with the intention of reevaluating their strategy. “When we started looking for VC money we just didn't know who to talk to, so we approached it in a haphazard way,” Altman said. “But then we learned enough to realize that we needed to approach things differently.”

The '03 Christmas holiday and most of January 2004 was spent revamping their fundraising approach. “We developed a method of cold calling much like a sophisticated salesperson would do,” Altman said. “We looked at who to call and how



Just five months after adopting their new strategy, Sequoia signed a term sheet for \$22 million.

Images courtesy of Sequoia Pharmaceuticals



to follow up. We were prepared for the meeting before we even made the calls in the event someone said to come in that afternoon.”

But adopting a sales approach was only the first step. In addition to following a coherent strategy, the executive team made what might have been its most important decision. They struck their business plan from their VC presentation in favor of a short 30-slide PowerPoint. “Of all the documents that we’d considered, this brief PowerPoint presentation showing the technical rationale, and outlining the results (of the data) was the most critical and effective thing we did in getting the attention of top-tier venture capital firms,” Altman said.

Just five months after adopting this new strategy, Sequoia signed a term sheet for \$22 million in venture capital financing.

### GenVec

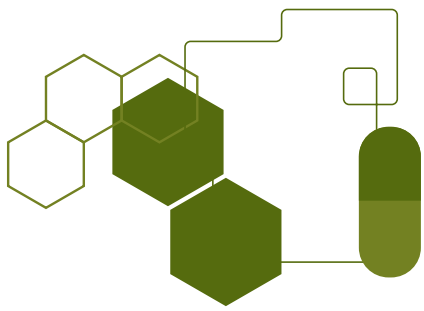
Many therapeutic companies are lean and focused, with an almost clairvoyant vision of the future, moving along a carefully laid path that, they hope, leads to an NDA and FDA approval. Often, however, emerging therapeutic companies find that they must be opportunistic.

And so it is that GenVec, once exclusively a gene-therapy company, finds itself developing not only gene-based medicines but also novel vaccine candidates, both based on the company’s proprietary adenovirus vector technology. “Vaccine commercialization was not part of our bigger plan,” says Paul H. Fischer, Ph.D., President and Chief Executive Officer of GenVec since 1996. “It was opportunistic. The federal agencies came to us because of our adenovirus core

technology.” As a result, GenVec is working on projects with multiple federal agencies including the National Institute of Allergy and Infectious Disease, the U.S. Department of Agriculture, the Department of Homeland Security, and the Naval Medical Research Center, in medically important areas like HIV, malaria, and foot and mouth disease.

While GenVec’s adenovirus technology has opened new and unforeseen doors for the company, it has also allowed the company to expand and grow its infrastructure in support of the company’s core areas. “We’ve all gained. For GenVec, it has meant expanded operational and scientific capabilities,” says Fischer. When it’s not developing vaccines, GenVec is in the business of developing and testing specific treatments for various cancers, heart disease, and macular degeneration. In macular degeneration, for example, GenVec’s technology delivers a gene to the retina where pigment epithelium-derived factor, or PEDF, is expressed, inhibiting abnormal blood vessel growth and protecting photoreceptor cells. The gene is packaged in an adenovirus vector and delivered by intravitreal injection. Phase I clinical trials—led by Johns Hopkins researchers and recently reported in the journal *Human Gene Therapy*—showed that the therapy can successfully slow the progression of neovascularization in subjects with advanced age-related macular degeneration (AMD). With retinal degenerative disease affecting more than nine million people in the U.S., the potential for the therapy is extremely large. Clinical trials are continuing in patients with less serious disease.

In its usual line of business, GenVec leverages its capabilities through strategic alliances and business arrangements with other companies. One such collaboration is with the Cordis



Corporation, a division of Johnson & Johnson. Cordis manufactures specialized cardiac catheters through which GenVec's experimental cardiovascular product is delivered to heart muscle for increasing vascularization. For international clinical studies, as with GenVec's oncology product TNFerade™, the company looks to the expertise of foreign-based contract research organizations.

How does GenVec manage the many and varied partnerships? Fisher finds that the answer is "to spend a lot of time on each. Senior management, project managers, and research teams get together frequently." It is especially helpful, says Fischer, that the company is located in the geographic vicinity of its vaccine partners. Personal contact, and the relationships that develop, enhance the partnership, he finds.

It isn't always easy though, for a variety of reasons, including the negative image that some people hold about gene-therapy. Fischer has found that changing the public's perception of the company's technology, and Wall Street's perception in particular, has become an integral part of everything the company does. "GenVec is not in the business of gene transfer, which is the technology that frightens some people. GenVec does not repair genes. We introduce a gene into a discrete tissue where it briefly produces a therapeutic protein.



It is hard to get people to understand the difference, so we address it often." What's helped the most? "We persist in providing facts as the data continue to evolve. Research articles in scientific publications, like the one in *Human Gene Therapy*, have been critical for reinforcing the safety of our technology platform."

In the end, Fischer advises stepping through doors when the right ones open. GenVec has been fortunate in that some of their opportunities have come with low risk and high potential reward. "There is a big upside if products evolve out of the collaborations, but not the least of the gains for biotechnology companies is the impact on manufacturing capabilities and scientific knowledge."

Leading Therapeutic Products Based on Revenue | DEVELOPED BY PUBLIC BIOSCIENCE COMPANIES HEADQUARTERED IN MARYLAND

TRADE NAME	COMPANY	THERAPEUTIC AREA	2004 Actual USD (millions)	2005 Actual USD (millions)
Synagis	MEDIMMUNE, INC.	Infectious Diseases	943.0	1,063.0
FluMist / CAIV-T	MEDIMMUNE, INC.	Infectious Diseases	48.0	21.0
Remodulin	UNITED THERAPEUTICS CORPORATION	Cardiovascular	66.0	110.0
Ethylol (amifostine)	MEDIMMUNE, INC.	Cancer	92.0	96.0
Gliadel	GUILFORD PHARMACEUTICALS (acquired by MGI Pharma Q4 2005)	Cancer	27.7	33.7

SOURCE: Infinata Market Research



When the board of directors at Osiris Therapeutics appointed Randal Mills president and CEO in July of 2004, they did so with the knowledge that while Mills might not be a world-class scientist, he was a guru at commercializing technology. As a matter of fact, Mills has never worked a single day as a research scientist. And while he does hold a Ph.D. in drug development, he readily admits that he really only pursued his doctorate as a means of gaining credibility among his scientific peers. The real motivator for Mills has always been the end result.

Applying a pragmatic approach to the organizations he's been involved with over the last 10 years has left a string of successes in his wake. Since beginning his career at the University of Florida Department of Orthopedics, Mills played instrumental roles in the creation of the University of Florida Tissue Bank, now called the Southeastern Tissue Alliance, one of the largest and most successful non-profit tissue recovery organizations in the world, as well as Regeneration Technologies, the for-profit spin off, which had a successful initial public offering in August of 2000. Most recently, Mills has applied his skills turning around Osiris Therapeutics, the Baltimore, Md. biotech known for its adult stem-cell based therapies. In addition to initiating five clinical programs and launching the company's first product, Mills worked with the company's chairman to secure \$70 million in financing for the company. Recently, MdBio had the opportunity to sit down with Mills to discuss his views on "best practices" for emerging therapeutics companies. The following are some of the highlights of the discussion:

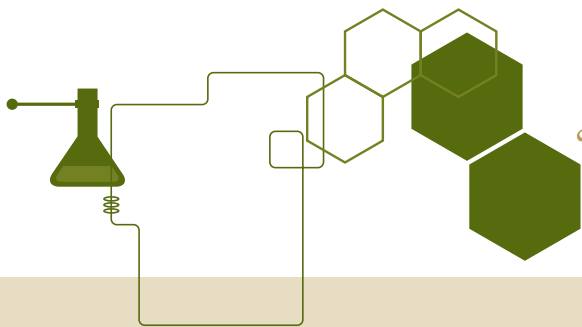
**Q: In 1997 the for-profit entity Regeneration Technologies spun off from a non-profit entity you played an instrumental role in creating, the University of Florida Tissue bank. What was the thinking behind the split?**

**A:** The reason we made the decision to split the company was fairly simple. First, by splitting the company into functional units, we were able to focus on the areas that were most relevant to each organization. And so the University of Florida Tissue Bank, later becoming Southeastern Tissue Alliance, was able to focus solely on the recovery of tissue. And RTI (Regeneration Technologies) was able to focus on the customer—the recipient of the tissue—and make sure that the products they were making were the best possible products, the safest possible products, and the most efficacious products. So by splitting, each company was able to have its own clearly defined mission.

In addition, there was at that time a real need at RTI, which dealt with the very high-tech engineering of human tissue, to be able to go out and raise the capital that the company needed to become and remain a top-tier company in the tissue engineering industry. Without the for-profit side being able to go out and raise capital from private and public investors, the company wouldn't have been able to afford the technology that was necessary to give the patients the best, safest product they needed.

**Q: It must be very challenging splitting an organization like that.**

**A:** First, I wouldn't recommend splitting a company. We had to, and in retrospect it was the right decision, but it's not a pleasant decision. It's not a pleasant decision nor is it a pleasant experience to go through. The company at that time had roughly about a hundred people or so. Many of those people had been together a while and when one family gets pulled apart into two, you know there's going to be uneasiness among the employees as to whether they were going with the good side, or were they going in with the not so good side—was there an A team, was there a B team, etc? The emotional aspects to this, as you might very well imagine, were very real and very significant. Splitting a biotech company is a very difficult thing to do. Logistically, it was pretty clear. You're trying to separate what goes where and why and for the most part things just fall into place, but the thing I remember most about it was who goes where and why. It was a really painful process, personally.



“If you are an unencumbered company, your

**Q: The pain must have been somewhat eased by the fact that three years after the spin off, Regeneration Technologies went public through an \$80 million IPO.**

**A:** Well, we raised a fairly significant amount of capital but I would argue that perhaps it wasn't a completely positive thing because it took our eye off the ball a little bit. Prior to that time I think we were a very lean, very well focused, hungry company that was doing all the right things to become a large, successful commercial entity and having a lot of money really ended up creating distractions. Also the transformation from a privately held company to a public company was something culturally that the company wasn't ready for.

**Q: In what way?**

**A:** Generally speaking, prior to the IPO, our company was the kind of company where you were free to do what you thought was best for the company and you could be as public about things as you wanted to be. There weren't a lot of rules. So frankly, it was an easy environment to work in. Suddenly, we were placed in this public spotlight where we were under far more scrutiny. Financial issues aside, we now had restrictions on communications and that was a shock to the company.

This had been a company that was proud of what it was doing and proud of its accomplishments. So to have somebody in the company that is really proud of what they did, and you have to tell them, “well you can't tell anybody about this great thing that you just did, because now that's insider information,” well, that type of restriction on communication was difficult for people in the company to swallow. And I think that this is particularly true in bioscience companies where, among the scientists at least, there is a tradition of publication and sharing information.

Also, prior to that time I would say we had a pretty long-range vision. Obviously we were a hungry company. We were doing smart things and making good decisions. As soon as the IPO came, that switched to a quarter-to-quarter type of vision, because now we were being watched by the street, and the street chops up the year into quarters, where you either perform or don't perform in a quarter. I really believe it is an unfortunate view for a biotechnology company to have, because there is not much biotechnology that can get done in a 3-month time frame.

**Q: How did RTI management handle these challenges?**

**A:** You know, some were easier to get through than others. Fixing the habit of talking about what we did and being very open and proud of what we did, well, that kind of took care of itself. The insider trading laws are scary enough that even if the employees didn't understand them, they knew they didn't want to have anything to do with them.

The quarter-to-quarter issue was a little bit more difficult, and it's obviously not unique to RTI. It is something that every publicly traded company has to deal with. It's a fact of life that as a publicly traded company you get evaluated on a quarterly basis. It's just so easy for companies to get caught thinking short term, and I believe it's imperative that you maintain a long-range view and make decisions that are in the best interest of the long-term value of the company as opposed to the near term.

**Q: Can you give an example of a strategy that you see companies employing to address short-term needs that negatively impact the long-term health of a company?**

**A:** I will give you a real-life example of something that my experience at RTI taught me a lot about and significantly influences my thinking going forward, and that's partnering. For a company like RTI, partnering was a way to have near term performance at the expense of the long-term good. We came out of the gate with a partnering model in place unfortunately, and then needed to really spend the rest of the time unwinding it. I think many partnerships between small companies and big companies are fundamentally flawed in that the interests of the two companies are often very different. And when you have competing or conflicting interests, you end up with a partnership that's almost doomed to fail from the beginning.

**Q: But don't a lot of big pharmaceutical companies use smaller companies to fill out their product pipeline?**

**A:** I think the word “use” is correct, which is why I'm sort of making the argument that if you're a smaller company with technology, don't bite the bait. I think that the pendulum is swinging such that the street is more often saying to these little companies “if you can find a way to do what you need to do without partnering, you might be better off.”

# value is inherently higher, especially if you have multiple technology platforms.”

## **Q: Why is that?**

**A:** If you are an unencumbered company, your value is inherently higher, especially if you have multiple technology platforms. For example, let's say you have two drugs. You partner with one company on one drug, and another company for the other. What's left to acquire, if at the end of the day they are just going to be serving two of their competitors? Clearly the unencumbered company from an acquisition standpoint is more attractive, and therefore creates greater value. That's one idea.

The second concept is speed. Partnerships with large companies are inherently slow. Not always, but usually the smaller company is more nimble. A lot of it has to do with the risk aversion associated with the larger companies. I'm not saying risk management is not important for all companies, but generally speaking, smaller companies and larger companies have different risk profiles when it comes to the commercialization of technology. Larger companies are more likely to send key decisions through rounds and rounds of analysis whereas a small company working on its own can be far more nimble. Clearly with Osiris that's been our experience.

The last thing is focus. So far at Osiris, the products we're bringing to market represent 100% of our focus. If we were to go out and partner with a large drug company for our auto-immune-disease candidate for example, it might be 100 percent of our focus, but it may only be five percent of their focus.

## **Q: So are you saying that big pharma is setting itself up for a fall, down the road?**

**A:** Oh, I don't think so because at the end of the day they can always just acquire the company if they really like its technology. However, this idea that you're going to get the milk for free, and not have to do anything with the cow, certainly goes on every day, but I think it's changing.

If you believe in your technology, the only way to control your own destiny is to sell your products yourself. In the instance of RTI, unwinding their partnerships may impact near-term revenue, but they're making that short-term sacrifice for the long-term success of the company. I think it is an excellent, value-creating decision.

Clearly I have a strong bias against partnering. And while some certainly do make sense, at Osiris we are not currently interested in additional partnerships.

## **Q: Is that a result of the success you've had in raising capital? If you hadn't just raised \$70 million would you still feel that way?**

**A:** Absolutely. I fundamentally believe that if your technology is really good, and you have a good plan, great people, and loyal investors, then you can raise money.

## **Q: Let's talk a bit more about Osiris. Here's a company that's been around for quite some time, and has seen its share of ups and downs. If I'm not mistaken, you joined the company in what could be considered a down period, yet you were able to turn the company around and quietly raise \$70 million.**

**A:** Yes, when I got to Osiris the company certainly had its troubles. The company had been around for 12 years by the time I arrived. I think you'd be challenged to find any company that's been around for 12 years that hasn't had its ups and downs. But clearly, when I came in, it was following a down period.

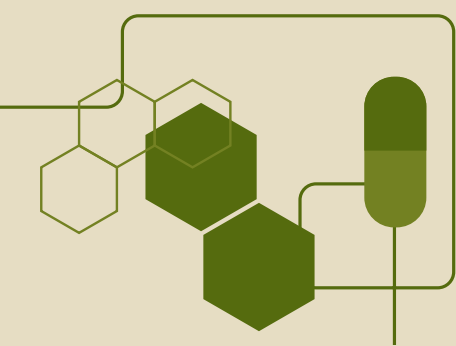
As far as the financing goes, our Chairman, Peter Friedli, did a tremendous job.

## **Q: So how did you turn things around?**

**A:** The first thing we did was to take a look at the company and figure out what we had that was valuable and then create a plan for extracting that value. It's really just a case of saying, "okay, what can we commercialize and when? And for how much?"

## **Q: Identifying value and extracting value can be two very different things.**

**A:** They are, but we were able to do both at Osiris. In order to do that, I must tell you, we needed to fundamentally change the culture of the company. I would argue that one of the most critical aspects facing any biotechnology company is the culture. The culture of a biotech company has to fit its mission. I think one of the fundamental problems that Osiris had when I got to it was its culture. The culture was clearly at odds with the mission that the company needed to have. When you're a biotech company and you've been around for 12 to 14 years, you need to be a commercially-driven entity.



**Q: And the company's culture wasn't commercially oriented?**

**A:** The culture that existed at Osiris when I arrived was more of an academic culture, and we needed to change that. Eventually we did—through a whole lot of communication and explaining. You see, we had very smart people at the company, there's no doubt about that. But we needed to demonstrate to them why it was important that we change gears from being the company that had spent most of its time focused on research to one that really needs to use all that brain power and all that energy and all that effort to get products to market. We had a lead investor that was so supportive that the company had been almost lulled into this sense of “well, it's okay, he'll just keep raising money and we'll be a research institution forever.” But investors put money in because they expect a return. So that's what we had to do. We had to change the culture, and once we did that, other things started falling into place.

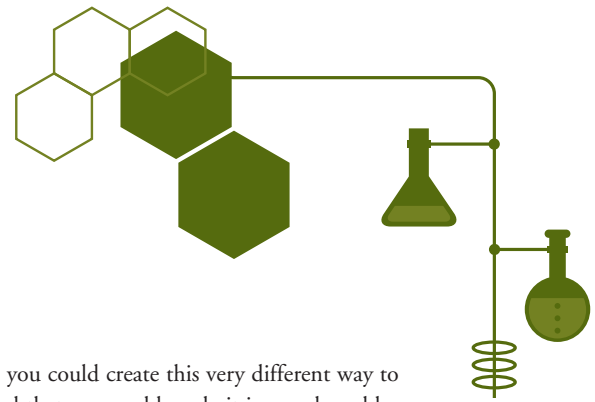
**Q: Can you give me an example of how things started falling into place?**

**A:** Osteocel's a great example. This was a case where some really bright people in the company wanted to commercialize a product, and had an idea how to do so quickly. That idea was presented in November, and in July that product was on the market. It's being used in people today, and the demand for that product greatly exceeds our ability to supply it, so we're working to overcome that. But it was that fundamental change in culture that led to people thinking differently and eventually led to different actions.

Ultimately this goes back to raising money, because you raise money with a solid plan and a team that can get you there. If you don't have those things, you're not going to be able to raise money. At Osiris, that solid plan evolved from the cultural shift within the company. You know, it's the same technology that existed before, but it's how that technology was going to be applied and the sense of urgency with which things were going to be pursued that made all the difference.

*NOTE: Following this interview but prior to publication, Osiris Therapeutics had a successful \$39 million IPO, and is now a public company.*





## Avalon Pharmaceuticals

Since its inception, Avalon Pharmaceuticals has received tremendous support from the financial community. Less than one year after incorporating in 1999, and without having performed even one scientific experiment, the company successfully raised \$10 million in venture capital financing, a nearly unheard-of feat in the sphere of bioscience investing. Just 18 months later, the company raised another \$70 million, which at the time was the largest early-stage venture capital investment in the history of biotech.

Then, in September of 2005, in the midst of an extremely dry IPO market, the company went public using W.R. Hambrecht's Open IPO Dutch auction system, a relatively new innovation in the IPO market that Avalon cofounder and current CEO and President Ken Carter believes played a key role in the company's successful offering.

"Hambrecht convinced us that the auction process was a really great way to go because it would allow us to make a decision based on the actual market for our stock," Carter said.

The Hambrecht Open IPO auction system, similar to the process made famous by Google in 2004, works by having investors log onto a specified website, making a 24-hour commitment for a specific number of shares at a specific price. This provides companies the benefit of gauging exactly what they will net on the day of the IPO. "And that's really unusual for IPOs. There's usually just old fashioned phone calls and bartering about prices among a small clique of investors and bankers that know each other," Carter said, "With Hambrecht's Open IPO system, anybody on the planet can go to the website and say 'if these guys go public tomorrow, I commit to buying X numbers of shares at X price.'"

When Carter and his four founding partners started the Germantown, Maryland-based company, they did so with the knowledge that Carter's extensive experience managing gene mapping projects in both academic and commercial settings would allow it to apply a systems biology approach to the discovery of new drugs, particularly in the area of cancer. "We wanted to do something novel with genomic information, taking it to the next level in terms of really incorporating large amounts of information into all stages of drug discovery," Carter said. "So while the support we've received from the financial community has been extremely gratifying for us, I think even more gratifying was the fact that we had really set

out to show that you could create this very different way to discover drugs and that you could apply it in a real world situation and show that it has some real advantages over traditional technology."

One of Avalon's key co-founders, Alan Walton, a Senior Partner at Oxford Bioscience Partners, invited Carter to a think tank meeting he was holding in Bermuda, out of which came the vision for what eventually became a new company. Upon returning from that Bermuda meeting, Walton and his firm took an active role in refining the company's business plan, something Carter says few venture capital firms have the skill or the desire to do at such an early stage. "Most of the time, entrepreneurs hobble along, pulling together their first hundred thousand dollars before VC's get involved," Carter said. "And the VCs that come in at that point aren't nearly as active as Alan and Oxford were with us." Oxford helped Avalon define its vision, and brought some very specific ideas—both scientific and corporate. In addition, Oxford provided the seed money to get Avalon up and running, and acted as lead investor in Avalon's \$10 million Series A round.

While having a VC firm's participation and support at such an early stage certainly has its benefits, it also has its costs. "In the end it did force us to be flexible in some of our valuation ideas," Carter said. "But Alan brought so much more to the party, it allowed us, I think, to see a vision that would grow the company in a very successful way."

According to Carter, inflexibility on equity and valuation is one of the major reasons many entrepreneurs fail. "I think many great ideas and potentially good entrepreneurs never make it out of the starting blocks, or stumble very early in the process because they have an inflated view of what their idea or asset is worth," Carter said. "The market is what it is, and you can either accept that people will invest in your idea at a given price, or you can not accept it and not accept their investment. A lot of entrepreneurs end up owning 100 percent of nothing, instead of a smaller percentage of something."

It wasn't until examining the company's burn rate in 2004, and realizing the need for another round of financing, that Avalon's leadership began serious consideration of a public offering. "It was at that time that the Board made what I thought was actually a very mature decision. We recognized that if we were going to realize our vision to develop the company into a

mature discovery and development company, we were going to need, over the next four or five years, access to a whole new level of capital. We felt that money would be much more accessible in the public markets than it was in the private markets,” Carter said. “We already had very good relationships with a number of different banks on Wall Street, so we started talking to them about what IPO opportunities might exist for Avalon in what was, and still is, a very tight IPO market.”

One of the reasons for Avalon’s excellent relations with Wall Street was Gary Lessing, the company’s chief financial officer. Avalon hired Lessing after raising their \$70 million Series B, recognizing the value of hiring a well-connected CFO. Previous to Avalon, Lessing had spent 14 years at Alex. Brown, working primarily in healthcare investment banking. “The day he walked in the door he started dialing every investment banker he knew,” Carter said. “So at least on a quarterly basis for the three years before we began the IPO process in earnest, he and I were up in New York or out in San Francisco or over in Baltimore, telling investment bankers our story. When we came to them and said ‘we’re ready’ there was no education, it was strictly a strategic discussion.” And with Avalon’s recent announcement of a \$7.25 million Private Placement, it looks like their strategy of accessing capital via public markets is working.

### **RegeneRx Biopharmaceuticals**

RegeneRx Biopharmaceuticals is not your typical publicly-traded biopharmaceutical company. They have no laboratories, little infrastructure, and only a handful of employees. What they do have is an innovative outsourcing business model, a market cap exceeding \$100 million, and a product well into phase II clinical development.

That product, Thymosin Beta 4 (T $\beta$ 4), is a synthetic copy of a naturally occurring human peptide that plays a vital role in tissue regeneration. The company is developing drug candidates based on T $\beta$ 4 in three principal areas: dermal, ophthalmic and cardiovascular wound healing. Originally isolated from the thymus gland, T $\beta$ 4 is found in high concentration in blood platelets, wound fluid, white blood cells, and in most other tissues of the body. It is widely involved in a variety of immune, cellular, and physiological processes, including regulation of actin polymerization, regulation of stem cell proliferation, angiogenesis, and anti-inflammation.

While conventional wisdom suggests that it is often a risky proposition staking an entire company’s future on the clinical success of just one molecule, RegeneRx CEO J.J. Finkelstein said he and his partners saw in T $\beta$ 4 the potential to expand into multiple therapeutic areas. “One of the interesting things about the technology is the fact that it has been established, pretty convincingly, that T $\beta$ 4 has a broad spectrum of potential therapeutic activities, from anti-inflammation to preventing apoptosis to inducing re-epithelization,” said Finkelstein. “And there are three or four other biological activities that may be important in a number of additional clinical areas. That’s what we’re trying to harness. We want to exploit each of those different areas.” And RegeneRx’s multi-pronged product approach may pay off. The company currently has three separate ongoing phase II dermal trials for T $\beta$ 4. Later this year, the company is planning a phase II ophthalmic trial, and a combined phase I/II cardiovascular trial.

In February 2001, the company secured an exclusive worldwide license from the NIH’s Office of Technology Transfer for all rights to T $\beta$ 4 for wound healing. To date, RegeneRx has filed more than 50 worldwide patent applications for other compositions, combinations, and clinical indications for the T $\beta$ 4 platform.

Expanding the company’s IP portfolio, however, was just the first step in the company’s turnaround. Seven years ago, when Finkelstein and others joined founder and current Chairman Alan Goldstein at RegeneRx, the company was basically dormant, with its stock trading at well under a dollar per share. While this was problematic in terms of raising capital, it did allow Finkelstein’s group to buy approximately 40 percent of the company at a bargain price.

After 13 months of restructuring, writing a business plan, and establishing critical milestones on which to base financing activities, the group settled on an outsourcing business model as the best strategy for achieving its goals. So far, the plan seems to be working, as the company’s market valuation has risen significantly since Finkelstein’s group took over, and RegeneRx has been able to raise over \$25 million.

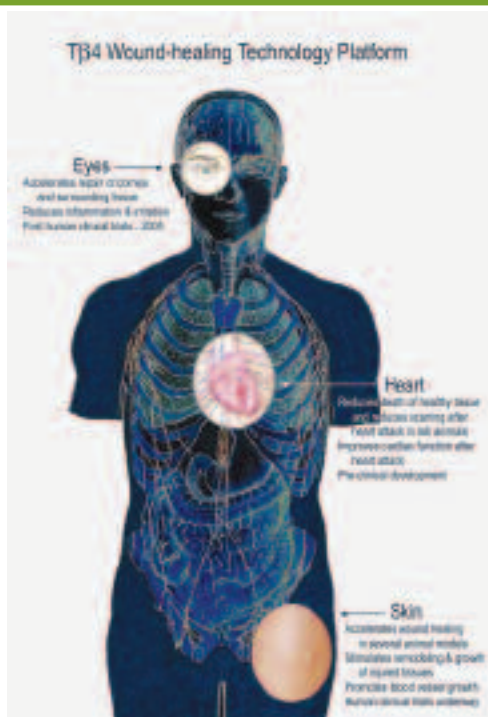
Most of that capital has been utilized in support of its clinical program. “Given what we wanted to do, there was no need for us to create an infrastructure to carry out all of the various tasks that are necessary to get a product from research and development into clinical trials and ultimately to the market place,” Finkelstein said. When the company wants to pursue a



RegeneRx Biopharmaceuticals is not your typical publicly-traded biopharmaceutical company. They have no laboratories, little infrastructure, and only a handful of employees.

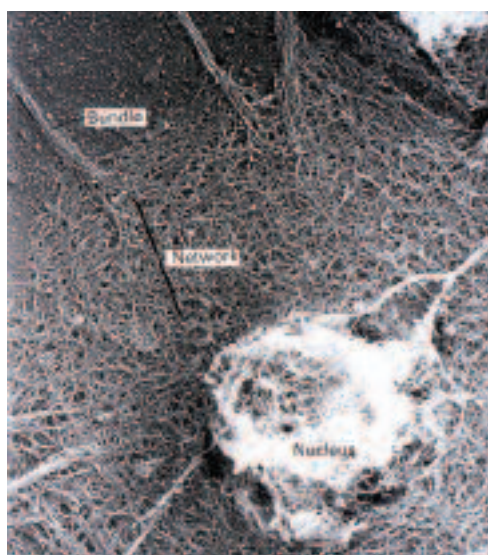
specific objective, they simply go out and purchase the resources they need. Virtually everything RegeneRx does is outsourced. “The jury’s still out on whether or not this outsourcing model is less expensive per clinical trial, but there is clear evidence to indicate that it can be more flexible and efficient,” notes Finkelstein.

While Finkelstein acknowledges that outsourcing is certainly not right for all therapeutics companies, he does believe for some it can be “an effective paradigm for developing a technology platform.” But, he cautions, hiring people who can implement a plan and manage the various vendors is critical to the model’s success. “Effectively managing all the different contractors working for us has been one of the most difficult aspects for us,” Finkelstein said. With proper experience and communication, though, Finkelstein believes most problems can be avoided. “One cannot assume that just because a company you contract with has a big name or has been around for a while, that they are always acting in your best interest. You have to manage them and make sure you communicate constantly and effectively.”



TOP: RegeneRx Tβ4 therapeutic targets

BOTTOM: Micrograph of actin filaments courtesy of RegeneRx





When Wayne T. Hockmeyer founded MedImmune, Inc. in 1988, he envisioned the tremendous potential of applying biotechnology to develop innovative medicines for a broad range of human conditions. Eighteen years and several products later, the company has evolved to become one of the largest biotechnology companies in the world. Today, MedImmune has a product portfolio spanning several therapeutic areas, a robust pipeline, and more than 2,200 employees working in facilities in Maryland, Pennsylvania, California, Kentucky, the United Kingdom and the Netherlands.

Dedicated to advancing science and medicine to help people live better lives, MedImmune is focused on the areas of infectious disease, cancer and inflammatory diseases. It is a fully integrated biotechnology company, involved in all stages of drug development and commercialization, including discovery research, clinical development, regulatory affairs, quality control, manufacturing, sales, marketing and distribution. With four actively marketed products, a promising pipeline of product candidates, and a rapidly expanding manufacturing capacity, MedImmune's leadership is not expecting the company's growth to slow anytime soon.

In March of 2004, MedImmune relocated its corporate headquarters to a new, state-of-the-art facility in Gaithersburg, Md. The 220,000-square-foot building, which currently houses more than 600 employees, was designed to emphasize the company's research function and enhance the collaborative potential of all departments within the organization. Upon completion of additional planned phases of expansion, the company expects its Gaithersburg facilities to one day include more than 750,000 square feet of office, lab and production space housing more than 2,000 employees.

According to MedImmune Chief Financial Officer and Senior Vice President Lota Zoth, the key to successfully managing such broad-scale operations lies in MedImmune's strong organizational structure, something that has evolved over time. "It is a very central component of the company's success," Zoth said, "particularly as we navigate through the explosion of growth that we've seen."

The growth Zoth refers to is due in large part to the extraordinary success of MedImmune's flagship drug, Synagis® (palivizumab), an injectable humanized monoclonal antibody for treatment of respiratory syncytial virus (RSV), the most common cause of lower respiratory infections in young children. Since receiving approval for Synagis in 1998 from the U.S. Food & Drug Administration (FDA), the company has seen revenues soar from \$227 million in '98 to more than \$1.2 billion in '05. A testament to MedImmune's innovative spirit, Synagis was the first monoclonal antibody successfully developed to combat an infectious disease.

In planning to launch Synagis, company executives were faced with the challenge of how best to get the drug into the hands of healthcare providers. Believing that the 60 sales and marketing people MedImmune employed prior to the launch of Synagis had little chance of meeting potential demand, the company forged a sales and marketing partnership with Abbott. "We wanted to have a partner that brought a lot of (drug) reps to the plate," Zoth said.

Today, MedImmune boasts a sales and marketing staff of more than 550 people supporting its current products, including Ethyol® (amifostine), FluMist® (influenza virus vaccine live, intranasal) and Cytogam® (cytomegalovirus immune globulin intravenous (human)) in addition to Synagis. In 2005, the company amended its agreement with Abbott to bring domestic sales and distribution of Synagis in house. A partnership with Abbott International still

"If you look back over the 18 years, critical decision one or two people," Zoth said. "Even into the

exists for international marketing of both Synagis and MedImmune's next-generation monoclonal antibody for RSV prevention, Numax™, currently in phase III clinical trials.

"Product distribution is critical," Zoth said. "We think about it daily and start planning as soon as a drug enters phase II trials."

Workforce expansion wasn't the only change brought about by the company's incredible success with Synagis. In the last several years, MedImmune has made key changes to its organizational structure, including an expansion of the base from which strategic corporate decisions are made. Zoth said that, until a short time ago, all decisions were made by the top few.

"If you look back over the 18 years, critical decision making was concentrated during much of that time among one or two people," Zoth said. "Even into the '90s there were still only three or four people making all of our strategic decisions."

At the beginning of this decade, that changed. An executive committee, now numbering nine people, was developed "to provide a diversity of viewpoints and allow us to better manage change within the company," Zoth said. She credits this committee with not only strengthening MedImmune's decision-making processes, but also with increasing employee "buy-in" once those decisions are made. At the time when Synagis was introduced to the market, the company had approximately six executives at the vice presidential level and higher. Today that number has grown to more than 40.

Eager to build upon the momentum of Synagis, MedImmune sought to add a second blockbuster drug to its product portfolio. In 2002 the company acquired California-based vaccine maker Aviron for its lead product FluMist, an intranasal vaccine for flu prevention in adults and children.

making was concentrated during much of that time among '90s there were still only three or four people making all of our strategic decisions.”

An immediate challenge facing MedImmune executives following the acquisition was how best to assimilate Aviron into MedImmune operationally, a complicated proposition given that FluMist was just months from anticipated FDA approval.

“Under normal circumstances, I think that it’s good practice to consolidate operations as quickly as possible,” Zoth said. “But with FDA approval of FluMist looming, we felt it was important to avoid disrupting the core operations at Aviron.” MedImmune has since moved substantially all former Aviron corporate operations to Maryland. “We were not achieving necessary synergies from the merger by continuing to have duplicate services on both coasts,” Zoth said.

In addition to the operational challenges, the Aviron acquisition presented unique cultural challenges as well. “West coast-based Aviron brought an interesting cultural diversity to east coast-based MedImmune that we had never had before,” Zoth said. “As a result we really had to reexamine our corporate values.” That process, Zoth said, led MedImmune to writing its first mission statement. Until that time the company relied on a list of nine “company values” to set the tone for MedImmune’s corporate culture. “And really they were more principles than values, somewhat left for people to interpret the underlying meaning for themselves,” Zoth said. “What was missing was the clear prevailing influence of core values that would have allowed us to consistently pull together as a cohesive team.”

So in 2004, a group of MedImmune employees worked to develop a mission statement, complete with a set of clearly defined values for the entire company to follow (see sidebar). In addition to stressing MedImmune’s commitment to helping people live longer, healthier and more

satisfying lives, the mission statement laid out four core values that are at the heart of MedImmune’s corporate culture.

“This was a significant cultural shift,” Zoth said. “For the first time our people were no longer left to their own individual interpretation of our corporate ideals.”

Although Zoth acknowledges that it took MedImmune 17 years to formalize its first mission statement, she believes companies, particularly biotech companies, are better served by doing so sooner than later. “I would encourage smaller companies to go through this process,” she said. “It’s important to define your corporate culture, especially when you are faced with explosive growth requiring multiple disciplines to work together as a cohesive team.”

But writing a mission statement is one thing; getting employees strategically aligned is another. To accomplish this goal MedImmune embarked on a year-long internal marketing campaign entitled “Spirit of Champions,” which included the creation of posters and handbooks as well as talking points for managers. Through company meetings and regular conference calls, MedImmune leadership ensured that the message was disseminated consistently at MedImmune facilities worldwide.

Zoth said the campaign was incredibly effective. “It was an important objective for us in 2005. When we graded our success, it received the top mark on our internal performance scale,” she said. “It really was outstanding.”



**In 2004, a group of MedImmune employees set out to define the company’s core values, which, in addition to the company’s corporate mission, have embodied MedImmune’s culture going forward:**

**Collaborative environment**

Interdisciplinary teamwork and mutually beneficial partnerships—both inside and outside the company—are essential to our success. We recruit, develop and retain a diverse, dedicated and teamwork-oriented workforce.

**Entrepreneurial spirit**

We value innovation, initiative and results. To avoid bureaucracy, we empower our employees and encourage flexibility. We act as owners—accountable for balancing risk, opportunity and responsibility.

**High integrity**

We value our integrity and strength of character. We conduct our business with honesty, respect and constructive communication.

**Strong work ethic**

We are driven by our passion for excellence. We value working hard in a smart way to maximize productivity and results.

COMPANY	THERAPEUTIC	TRADE NAME	INDICATION
<b>IND FILED</b>			
AnGes	HGF (Hepatocyte Growth Factor)	unknown	Heart Disease/Peripheral Vascular Disease Phase II
Celera Genomics	CRA-024781	unknown	Cancer/Tumors (Unspecified)
MedImmune	anti-RSV MAb	Numax	Viral Infection, Pneumonia
PharmAthene	Anthrax Vaccine	ToxBlox	Anthrax Exposure, Infectious and Parasitic Disease
<b>PHASE I</b>			
Acambis	Dengue fever vaccine	unknown	ChimeriVax-Dengue/Infectious and Parasitic Disease
Avalon Pharmaceuticals	AVN-944	unknown	Cancer/Tumors (Unspecified)
Celera Genomics	CRA-028129	unknown	Psoriasis and Psoriatic Disorders
DynPort Vaccine Company	vaccine, cell cultured smallpox	unknown	Infectious and Parasitic Disease, Unspecified Viral Infection
DynPort Vaccine Company	recombinant anthrax vaccine	Unknown	Vaccines Anthrax Exposure
DynPort Vaccine Company	botulinum neurotoxin vaccine	unknown	Vaccines
DynPort Vaccine Company	recombinant plague F1V vaccine	unknown	Vaccines Infectious and Parasitic Diseases
EntreMed	ENMD-1198	unknown	Solid Tumors
ExonHit Therapeutics	EHT 0202	unknown	Neurologic Disorders, Alheimers Disease
GenVec	Myoblast cell transplantation	unknown	Myocardial infarction/Congestive Heart Failure
GenVec	porcine liver cells	unknown	Liver Disease
GenVec	HIV vaccine	unknown	HIV Infection
GenVec	AdPEDF	unknown	Macular Degeneration
Human Genome Sciences	B-lymphocyte stimulator (BlyS)	Unknown	Immunodeficiency
Human Genome Sciences	Unknown	Albutropin	Growth Hormone Deficiencies/Abnormalities
Human Genome Sciences	unknown	LymphoRad	Multiple Myeloma, Lymphoma, Non-Hodgkins
Human Genome Sciences	659032 Genomics Derived Lipoprotein	unknown	Cardiovascular Disorders, Atherosclerosis
Human Genome Sciences	PA mAb	ABthrax	Anthrax Exposure, Bacterial Infection



COMPANY	THERAPEUTIC	TRADE NAME	INDICATION
Human Genome Sciences	HGS-TR2J	unknown, agonistic human monoclonal antibody to TRAIL	Solid Tumors
MedImmune	vaccine, cytomegalovirus; CMV vaccine	unknown	Vaccines, Viral Infection, Congenital Anomaly
MedImmune	siplizumab, MEDI-507	unknown	Lymphoma, Leukemia Unspecified
MedImmune	anti-IL-9 Mab	unknown	Asthma
MedImmune	RSV/PIV-3 vaccine	unknown	Vaccines, Viral Infection
MedImmune	MEDI-545	unknown	Systemic Lupus Erythematosus
Nabi Biopharmaceuticals	S. epidermidis vaccine	unknown	Skin Infections/Disorders
Nabi Biopharmaceuticals	S. aureus type 336 vaccine	unknown	Staph Bacterial Infections/ Infectious, Parasitic Disease
Osiris Therapeutics	mesenchymal stem cells	Provacel	Heart Disease, Myocardial Infarction
Otsuka America Pharmaceutical	OPC-51803	Unknown	Nocturia (Frequent Nighttime Urination), Incontinence
PharmAthene	MDX-1303	Valortim	Anthrax Exposure/Bacterial Infection
Rexahn	RX-0201	unknown	Solid Tumors
United Therapeutics	beraprost	unknown	Pulmonary Hypertension

PHASE I/II

EntreMed	2-methoxyestradiol	Panzem	Breast Cancer, Multiple Myeloma Prostate Cancer, Ovarian Cancer
Human Genome Sciences	HGS-ETR1, TRAIL-R1 mAB	unknown	Cancer/Tumors (Unspecified), Lung, Colorectal Cancer, Lymphoma, Non-Hodgkins and solid tumors
Iomai	TIM ETEC vaccine	unknown, Transdermal patch vaccine	Diarrhea
MedImmune	LM-609	Vitaxin	Solid Tumors, Colorectal Cancer,
MedImmune	LM-609	Vitaxin	Solid Tumors, Colorectal, Prostate, Melanoma
Nabi Biopharmaceuticals	immune globulin	Civacir	Hepatitis, Viral, C/Liver Transplant Surgery
Osiris Therapeutics	OTI-030	Chondrogen	Knee Replacement
Otsuka America Pharmaceutical	OPC-41061	Unknown	Congestive Heart Failure, Kidney Disease, Hyponatremia
Sucampo Pharmaceuticals	SPI-8811	unknown	Cystic Fibrosis
VIRxSYS	VRX496	unknown	HIV Infection

Clinical Trials by Phase | 2005-2006 CONTINUED

COMPANY	THERAPEUTIC	TRADE NAME	INDICATION
<b>PHASE II</b>			
Acambis	vaccine small pox, ACAM2000	unknown	Viral Infection
Acambis	unknown	ChimeriVax-West Nile vaccine	Viral Infection
Acambis	vaccine, typhoid	Holavax-typhoid	Bacterial Infection/ Diarrhea
Acambis	vaccine, H. pylori	unknown	Helicobacter Pylori/ Gastric Ulcers
Acambis	C. difficile vaccine	CdVax	Bacterial Infection/ GI Diseases/ Diarrhea
ExonHit Therapeutics	pentoxifylline, EHT0201	unknown	Amyotrophic Lateral Sclerosis (ALS)
Human Genome Sciences	unknown	Albuferon	Hepatitis, Viral, C
Human Genome Sciences	unknown	LymphoStat-B	Systemic Lupus Erythematosus, Rheumatoid Arthritis
MGI Guilford Pharmaceuticals	GPI-1485	unknown	Parkinson's Disease, Erectile Dysfunction
MGI Guilford Pharmaceuticals	unknown	Dopascan Injection	Parkinson's Disease
Nabi Biopharmaceuticals	vaccine, nicotine conjugate	NicVAX	Tobacco Dependence
Nabi Biopharmaceuticals	hyperimmune globulin	Altastaph	Pediatric Staph Bacterial Infection
Osiris Therapeutics	OTI-010	Prochymal	Graft Versus Host Disease
Otsuka America Pharmaceutical	OPC-14523	Unknown	Depression, Bulimia, Obsessive Compulsive Disorder
Otsuka America Pharmaceutical	OPC-28326	Unknown	Peripheral Vascular Disease, Raynaud's Disease
Panacos, Inc.	PA-457	unknown	HIV Infection
RegeneRx Biopharmaceuticals	Thymosin beta 4, TB4	unknown	Wounds/Skin Infections
Spherix	tagatose	Naturlose	Diabetes Mellitus Type 2
Sucampo Pharmaceuticals	FK-506, tacrolimus	unknown	Eye Disorders/Infections
<b>PHASE II/III</b>			
GenVec	unknown	TNFerade	Pancreatic Cancer, Melanoma

COMPANY	THERAPEUTIC	TRADE NAME	INDICATION
---------	-------------	------------	------------

PHASE III

Acambis	vaccine, yellow fever	Arilvax	Vaccines
Acambis	unknown	ChimeriVax-JE	Cerebrovascular Disease, Unspecified
Advancis	unknown	amoxicillin PULSYS	Bacterial Infection/ Pharyngitis
MedImmune	MEDI-517	Cervarix	Viral/Vaginal Infection, Cervical Dysplasia/Cancer
Nabi Biopharmaceuticals	Staphylococcus aureus vaccine	StaphVAX	Staph Bacterial Infections
Nabi Biopharmaceuticals	hepatitis B immune globulin	Nabi-HB	Liver Transplant Surgery, Hepatitis B, Viral
Otsuka America Pharmaceutical	OPC-6535	Unknown	Ulcerative Colitis
Panacos, Inc.	Unknown	Inactine	Anemia, Cardiovascular Disorders

PHASE III COMPLETED/FDA APPROVED

MedImmune	amifostine/cisplatin/vinblastine	Ethiol	Lung Cancer
MedImmune	trimetrexate glucuronate/leucovorin	NeuTrexin	Pneumonia
MedImmune	CAIV-T	FluMist	Pediatric, Influenza
MedImmune	palivizumab	Synagis	Pediatric Congenital Heart Disease, Infectious and Parasitic Disease
MGI Guilford Pharmaceuticals	polifeprosan 20/carmustine	Gliadel	Brain Cancer
Sucampo Pharmaceuticals	lubiprostone	unknown	Constipation/Irritable Bowel Syndrome/Ileus
United Therapeutics	treprostinil	Remodulin	Pulmonary Hypertension/Pulmonary Fibrosis/Peripheral Vascular Disease/Cancer

