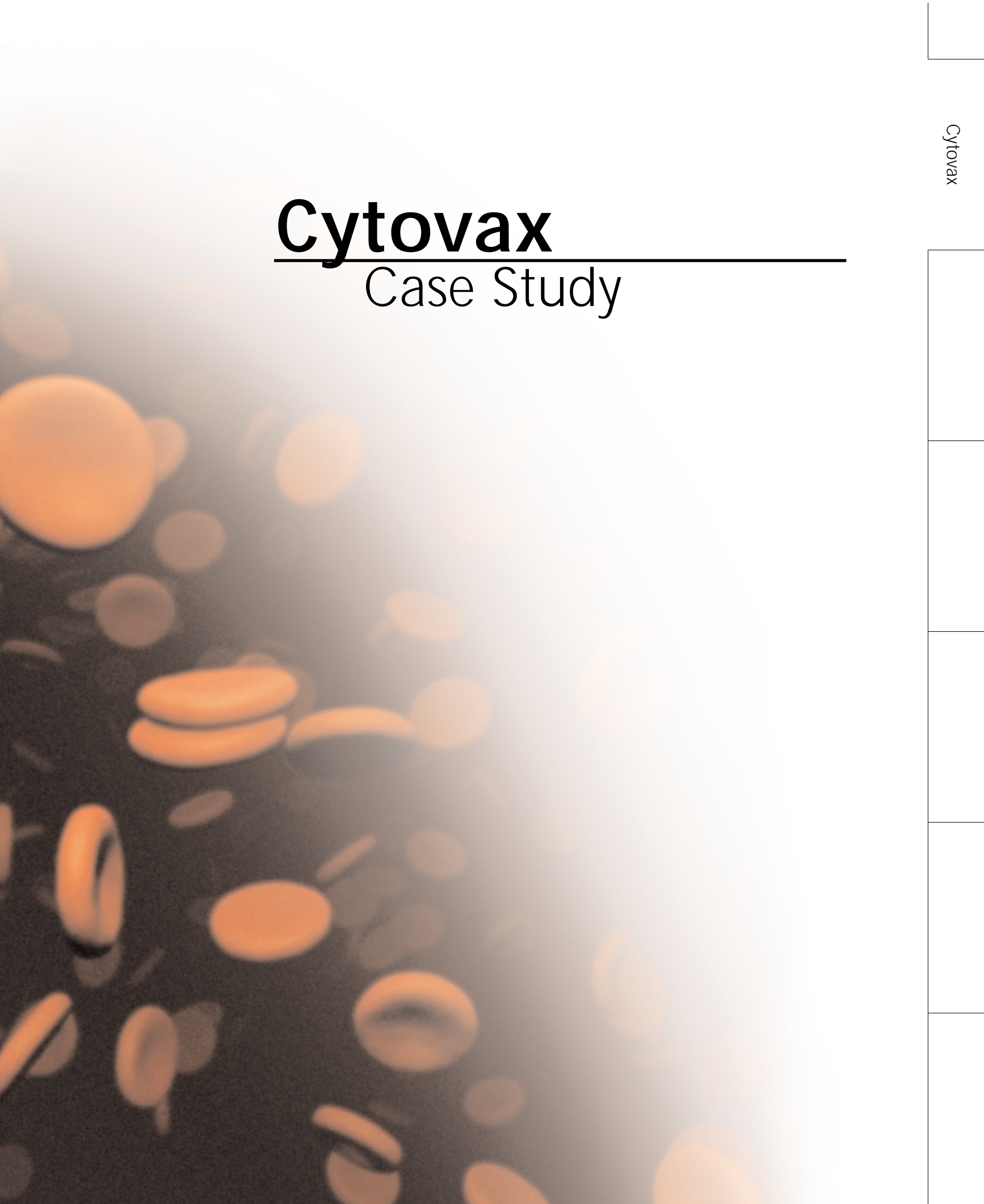


Cytovax

Case Study



Cytovax Biotechnologies Inc.

Managing Change

2001 was quite a year for Cytovax Biotechnologies Inc. The Edmonton-based biotech company raised in excess of \$20 million during the fiscal year, including \$10 million from its Initial Public Offering.

Cytovax began 2001 by making the transition from private to public company, culminating with a successful Initial Public Offering and concurrent listing on the Toronto Stock Exchange (CXB). It ended the year with another major announcement – the filing of a Clinical Trial Application with Health Canada to begin human clinical trials of its lead product Cytovaxine™. This marked the beginning of yet another transition for Cytovax – from a pre-clinical to a clinical stage company.

A successful year, by any measure. And one in which Cytovax board member and former Cytovax CEO Dr. Gerard Tertzakian takes particular pleasure. There was a time when the possibility of Cytovax aiming for such milestones – let alone reaching them – seemed remote.

“Cytovax began as a typical university spin-off,” explains Tertzakian. “It had a brilliant idea which was developed to a stage that was enough to spin a company around it. But the company had no outside managers, no space outside the university, and no outside directors. And as a result they had essentially no outside financing.

“The company had to change in fundamental ways for it to have a chance of success.”

Building the business

In 1986, AHFMR's Technology Commercialization (TC) Program supported University of Alberta biochemistry professor Dr. Robert Hodges as he investigated the feasibility of commercializing his research on peptides. A company, Synthetic Peptides Inc. (SPI), was subsequently established. By 1991, SPI had moved the technology farther along, and a project to test a synthetic peptide vaccine was also supported by the TC Program.

But while technology development continued, company development had come to a virtual standstill. Hodges recognized the problem and asked Tertzakian for help. Tertzakian is a well-known figure in the biotechnology community in Alberta and Canada. He has more than 30 years of experience leading a number of technology-based companies including Raylo Chemicals Inc.

“Money for further development was a critical problem at SPI,” says Tertzakian. “The money SPI had was not enough – it was all from local people, in relatively small amounts. I tried to raise money for them under these circumstances – no outside managers, no off-campus space, no staff, no outside directors – but couldn't. We wasted a year. I wish we hadn't.”

Tertzakian saw synergy between SPI and another small Edmonton biotechnology company, Biotex Laboratories Inc., which had also received TC funding from AHFMR. Cytovax was created in 1998 through the amalgamation of SPI and Biotex.

“When we joined SPI with Biotex, we created a company that had the potential to work,” says Tertzakian. He reluctantly agreed to be CEO, but only until financing could be obtained and an outside CEO hired.

Tertzakian's next job was building a board of directors. “You need a board that is not just made up of local people. You need international names who have connections and can pull some strings.

“In my earlier days I never thought that having a good board would be so important. To a large extent I thought you could do it all yourself. And if you put enough time and effort into it, you can. But why? There are people who are willing to give you that advice and information.”

One of the people Tertzakian targeted for the Cytovax board was Dr. Robert Fildes. He has more than 30 years of international experience with leading pharmaceutical and biotechnology companies. He has worked as a senior executive at Glaxo and Bristol-Myers Squibb, and as founding President of Biogen and President of Cetus Corporation. Fildes has been chairman of the Cytovax since the establishment of the company.





"Fildes has connections all over," says Tertzakian. "If he doesn't know the people we're looking for first-hand, he knows people who do know them. Instead of me taking six phone calls, he takes two calls to get the right person."

Once Cytovax had a corporate structure, decent office and lab space, and a good board, financing was much easier to obtain. The first round of financing was a private placement through Acumen Capital Partners. That was followed by a \$1.5 million venture capital financing from Royal Bank Ventures Inc. and Business Development Bank of Canada and a \$1 million convertible debenture financing from these institutions. (During fiscal 2001, these investors converted the entire amount of the outstanding convertible debentures and accrued interest into Class A voting shares.)

It was at this stage in late 1999 that Cytovax recruited Dr. Bin Huang, from Monsanto in Ontario, as the new CEO to succeed Tertzakian.

In November 2000, Cytovax announced the closing of the issue and sale of 1,976,000 Special Warrants. This private placement consisted of several sophisticated institutional investors and Cytovax's venture capital investors – Royal Bank Ventures and the Business Development Bank of Canada. It raised gross proceeds of \$7,904,000.

Finally...enough money to move ahead with technology development.

A look at the technology

Cytovax's proprietary technology has its roots in the pioneering work on synthetic peptides done by Dr. Robert Hodges at the University of Alberta. Hodges saw potential in using peptides (small molecules made up of amino acids linked together) as drugs. Based on years of developmental work, the Cytovax technology uses peptides to block the infection process. It works even if the bacteria are resistant to antibiotics.

This is an important point for scientists and investors alike. As Cytovax President and CEO Dr. Bin Huang notes, when she makes presentations about Cytovax it is always talk of "superbugs" that catches her audience's attention.

"People have heard a lot about antibiotic resistant bacteria, the so-called superbugs. These bacteria are causing progressively more infections in hospitals," says Huang. "They not only drive up the cost and length of hospitalization, they make people who are already sick much sicker and in some instances the infections kill people." According to 1995 data, hospital-acquired infections cost US\$4.5 billion and contributed to more than 88,000 deaths in the United States. And the problem has become worse in the past several years, leading to quarantines and closures of entire nursing units.

The increasing ability of bacteria to resist antibiotic therapy creates tremendous potential for Cytovax. Whereas antibiotics typically kill bacteria directly, the Cytovax technology blocks the infection process without killing the bacteria directly.

How does it work? Certain bacteria have extensions called pili; at the tip of each pilus is an "adhesin". The adhesin binds directly to a receptor site on a human cell – similar to a lock and key. Once the key is inserted in the lock, infection occurs. Cytovax vaccines and therapeutics interfere with the binding process, thus blocking infection.

The technology has the potential to be a major weapon in the fight against antibiotic-resistant bacteria. Cytovaxine™, the lead product, works against *Pseudomonas aeruginosa*, the most common cause of hospital-acquired infections. High-risk groups for *P. aeruginosa* infection are people with cystic fibrosis, cancer and AIDS, as well as patients in intensive care units, transplant patients and burn victims.

Moving forward

The Cytovax story has proven to be a compelling one for investors. The company's Initial Public Offering was completed in February 2001, raising \$10 million. Cytovax is now traded on the Toronto Stock Exchange.

"We never considered the IPO to be an end in itself," says Denis Taschuk, Vice President, Finance and Administration, and Chief Financial Officer. "The IPO was the commencement. We had no sooner closed our financing, then we were thinking about the next round."



Taschuk joined Cytovax in late 2000, and was a key addition to the senior management team. A Chartered Accountant, he has more than 15 years of experience including six years at a large public company. Managing Cytovax's transition to a public company has been part of Taschuk's job.

One of the first steps taken by the company was to develop a good regulatory infrastructure to deal with security commissions, stock exchanges, auditors, lawyers and investors. Cytovax has continuous disclosure obligations that require it to publish financial information on an ongoing basis and prepare disclosure documents in connection with meetings of security holders.

"There's a huge learning curve involved," says Taschuk. "Only a small number of people in the biotech community in Edmonton have public company experience. There are three ways to deal with that: develop our own expertise, use consultants, or hire expertise.

"By and large, the path we've chosen is to develop our own people in conjunction with a good group of advisors. It's important to have a strong support network around us."

Another key activity for the newly listed company was getting its story out to the investment community. One of Taschuk's major responsibilities is managing the public markets through meeting with investment dealers, brokers and analysts.

"We make sure that either myself or our CEO, or both of us, are introducing or reinforcing our story to a number of key players," he explains. "This is not stock promotion – it's making sure the investment community knows our story and making sure they're current on our story. When we have a major announcement, that is a good time to go and refresh peoples' memories about our story. So we do that. And we've done that pretty much from the time we went public."

Cytovax attends biotech conferences in Canada, US and Europe, sets up one-on-one institutional meetings and sessions with analysts, and attends retail luncheons. Getting the analysts' attention is vitally important, Taschuk notes. "The analysts are central to the investment brokerage houses understanding our story. They look to the analysts and ask: Do you understand the story? Do you believe these guys? Do you like the science? Is the stock valued fairly? Is it a good investment?"

Partnering has also figured prominently in Cytovax's evolution. In June 2000 the company entered into an agreement with Canadian biotech giant BioChem Pharma Inc. (BioChem Pharma has since merged with Shire Pharmaceutical Groups plc.) BioChem Pharma made an initial \$2 million investment in Cytovax and received a worldwide exclusive license to manufacture and market Cytovaxine, in addition to licensing options on other products. Besides the funding, Cytovax gained access to the larger company's considerable expertise in manufacturing, clinical trials and marketing.

Partnerships are critical, notes Tertzakian. "It's not that difficult to start a project like this. But getting to the finish...to fully developing and marketing a product...it's a stretch on your own. You need the partners who are already in this business, who have a marketing team and everything else that it takes to push a product past Phase III clinical trials.

"And that's what Cytovax is doing now. Shire is not the only one, they're looking at other options."

Tertzakian notes that technology partnerships may also be needed. "Partnerships are not only with giant marketing companies," he explains. "Sometimes you progress your technology to a certain point and then, to push it to the end, you need to do some technical things, genetic engineering for example. This genetic engineering pathway may be patented, the property of some other company. And you need that technology to fully develop your product."

How do you find partners? "Sometimes it's cold calling but usually you go through the network," says Tertzakian. "This is why it's so important to have a board that is well-connected.

"Experience counts because it comes down to a lot of horse trading. You say: I need your technology now and I'll give you a piece of the action when my technology is mature. Again, this is where the board of directors comes in. We have two people on the Cytovax board who have done this many, many times. Their expertise is vital."



Looking ahead

After dealing with the challenges of becoming a public company, Cytovax now prepares to face a new set of challenges. One of the key issues is maintaining its ability to advance the technology while at the same time moving the business forward.

Taschuk notes that the groundwork for a next round of financing was being laid even while the IPO process was underway. An important part of this process is setting – and achieving – performance milestones. Cytovax's two major milestones for 2001 were completing the IPO, and getting the clinical trial application filed for Cytovaxine.

“When you meet your milestones you develop credibility in the marketplace,” says Taschuk. “Then as you advance your product or products, investors say: we see your past performance, you were able to deliver, therefore you have credibility and we will support the company going forward.”

The second part of laying the groundwork for additional financing is having success with the products – something that Cytovax, as a preclinical company, hasn't had to deal with. However in January 2002, Health Canada approved Cytovax's application to begin a Phase I clinical trial for Cytovaxine.

The company's 2002 milestones reflect the new focus:

- Begin Phase I trials for Cytovaxine. Phase I trials are usually performed on healthy volunteers and investigate the safety of the treatment.
- Establish an agreement that will allow Cytovax to develop fully human monoclonal antibody therapeutics for the treatment of *Pseudomonas aeruginosa* infections. This therapeutic will be used to treat already infected patients.
- Commence preclinical research in a second target infection, which is expected to be *Streptococcus pneumoniae*. Each year people make nearly 30 million visits to doctors for earaches, of which one half are caused by *S. pneumoniae*. Data show that antibiotic resistance to this bacterium is approaching 50% in the United States.

Taschuk says that every time a company hits a major milestone, it tends to be a financing event. So he expects that Cytovax's next round of financing will be tied to a key event.

“Financing is always a key issue. We must make sure we've got sufficient funding to drive our products forward. Clinical trials are very expensive, and as you advance through the clinical trial process they become progressively more expensive.”

But money isn't the only issue. Managing the clinical trials process is another critical task. “We've never done this before,” says Taschuk. “We've got good people and feel very good about it, but it's a new experience. We have to maintain tight control over the entire clinical trial process.”

Another challenge is broadening the product pipeline – with Cytovax's existing technology or complementary technology.

Human resources will also be key to achieving the milestones. Cytovax is a small company with 26 employees, notes Taschuk. “We need to have the right people in place to continue to develop this technology and ensure products are going through clinical trials as they should be. As a very lean operation, we have to rely on outside people as advisors and suppliers. However this does make you vulnerable – you may lose control of the process at that point in time. We've spent a lot of time ensuring that we're surrounded by good-quality people.

“Not all this expertise needs to be in-house right now. But as we add product candidates to the clinical trial process, it will put more strain on outside resources. There will be a time when we have to bring some of the expertise in-house, whether it's clinical, regulatory or marketing.”

The ability to change

If there's one constant about the Cytovax story, it is change. And that's exactly how it should be, says Gerard Tertzakian.

"Companies aren't static, they must change, especially a young company like Cytovax. Every time something happens – whether it's obtaining financing, attracting a new partner, reaching a technology milestone – it sparks a change in the company.

"I was the CEO of Cytovax for two years. The company got to a certain point, and then it was time to put someone else at the helm. And as the company evolves, the board may have to change. A good board will be able to evaluate itself just as it evaluates the people in the company.

"These are difficult decisions, but they must be made. How well we manage the changes will, at least in part, determine our success."

