

Of Mice and MAbs: **MEDAREX**



Medarex has a lot riding on its compound ipilimumab (MDX-010), an anti-CTLA-4 antibody that is currently being studied in patients with metastatic melanoma either alone or in combination with vaccines or chemotherapy. With Phase 3 results expected later this year, 2007 will be a defining year for this biotech.

By Dianne S. Pena

One of the companies playing a role in the cancer vaccine story is not a vaccine company at all, but Medarex, Inc. (Nasdaq: MEDX), a biotechnology company focusing on the discovery, development, and potential commercialization of fully-human antibody-based therapeutics for cancer and other serious diseases. Its Phase 3 compound ipilimumab (also known as MDX-010) is being investigated for use alone or in combination with chemotherapy, immunotherapy and vaccines.

Since its founding in 1991 and initial public offering in 1997, Medarex has ridden the ups and downs familiar to biotech development companies. Today it is involved in over 40 collaborations and partnerships with pharmaceutical and biotech companies. It has a pipeline that many Big Pharma companies would envy. The engine driving the pipeline to develop fully-human antibodies is the UltiMAb Human Antibody Development System®.

Christian S. Schade, Senior Vice President, Finance and Administration and Chief Financial Officer, noted, “The purchase of GenPharm in 1997, which brought Nils Lonberg, PhD—a pioneer in the biotech application of transgenic animals—on board, turned out to be a seminal event in the evolution of Medarex.”

UltiMAb Technology

Early antibody products were fully murine, and as a result, were recognized by the patient’s immune system as foreign, with the potential to trigger an immune response leading to possible loss of efficacy, infusion reactions, and serious sequelae. Subsequent antibody technologies tried to address this problem by “humanizing” mouse-generated antibodies using chimeric and CDR-grafting techniques.

Although humanized antibodies were less immunogenic than fully murine ones, the development process was more cumbersome.

The humanizing process itself was also complicated, requiring time, expense, and finesse to minimize rodent residues while retaining antibody activity.



Nils Lonberg, PhD,
Senior Vice President and
Scientific Director

According to Dr. Lonberg, Senior Vice President and Scientific Director, fully-human antibodies have several advantages over earlier antibody technologies, including lower immunogenicity and a high affinity for antibody targets (up to 1,000 times higher than chimeric or humanized antibodies).

Ltd., to develop an additional human antibody-generating mouse, the KM-Mouse®.

“Another advantage of the UltiMab platform is that it lets us spend less time in lead optimization, while producing a fully-human antibody with better affinity for its target and low immunogenicity,” said Dr. Lonberg. “Once an antigen

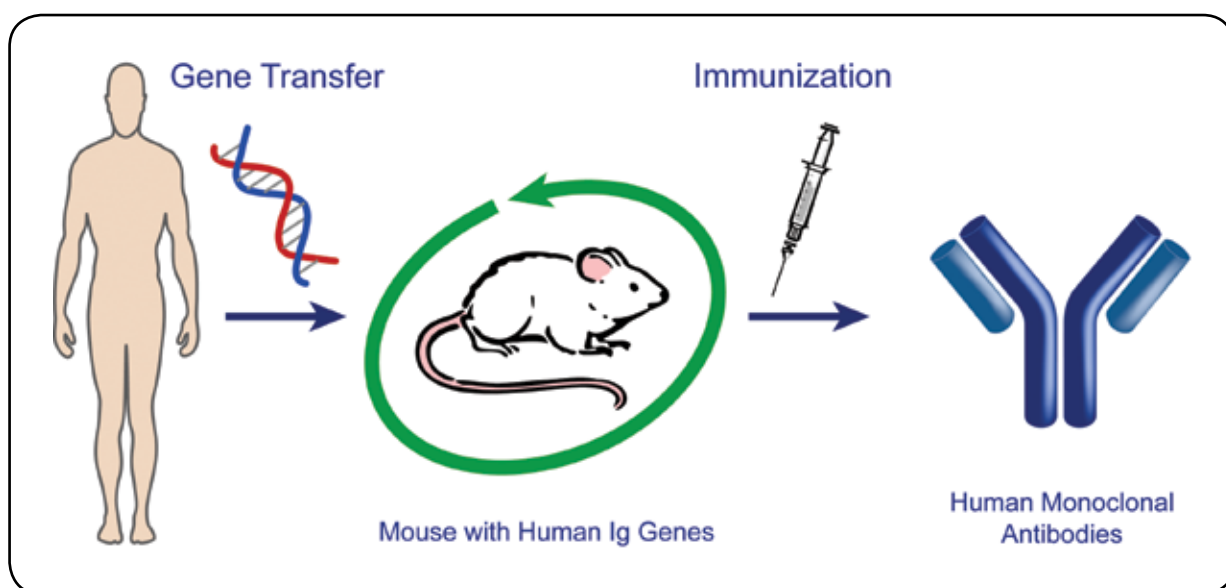


Figure 1: Medarex's UltiMab Technology. Reprinted with permission from Medarex Corporation.

Medarex's UltiMab technology uses a strain of transgenic mice, the HuMAB-Mouse® (see Figure 1). By suppressing the mouse's ability to encode its own antibodies, and replacing it with human genetic material for encoding antibodies, the mouse produces fully-human antibodies. This ability is passed along to its progeny. In addition to its proprietary HuMAB-Mouse, Medarex also has access to the Kirin TC Mouse™ and has partnered with the pharmaceutical division of Kirin Brewery Company,

target is chosen, the UltiMab System facilitates production of a variety of fully-human antibodies against various epitopes on the target antigen. These antibodies can then be tested to determine the best candidate before proceeding with further development, an approach that can reduce time and expense.”

As proof of this concept, over 30 antibody compounds derived via UltiMab technology are presently in clinical trials, [cont. on pg 46 >>](#)



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or have had regulatory applications submitted for such trials. As these compounds move through development, Medarex is entitled to a variety of milestone payments, licensing fees, and equity compensation, and, should commercialization occur, royalties. Most notably, several compounds developed using UltiMAB have reached Phase 3 trials. These include:

- Ipilimumab (MDX-010), an anti-CTLA-4 antibody currently being studied in patients with metastatic melanoma either alone or in combination with vaccines or chemotherapy (being developed in partnership with Bristol-Myers Squibb)
- Golimumab (CNTO 148), under development by Centocor for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis
- CNTO 1275, also being developed by Centocor for psoriasis
- Zanolimumab (HuMax-CD4™), being developed by Genmab/Merck Serono for cutaneous T-cell lymphoma

Leveraging Partnerships and Alliances

Funding development of this pipeline is no small matter. Medarex relies on partnerships, alliances, and licensing arrangements to generate revenue and fund development. Schade explained that Medarex has developed a two-pronged approach: out-licensing its UltiMAB technology and creating 50:50 collaborative partnerships.

Out-licensing the UltiMAB technology, including its HuMAB-Mouse, permits other companies to develop their own antibodies for testing and development. According to Schade, these arrangements yield milestone payments (an estimated \$7 to \$10 million per milestone) and a 3% to 5% royalty in sales should commercialization occur.

With 50:50 collaborative partnerships, Medarex partners with companies or institu-

tions that have identified potential therapeutic targets or have created platforms for identifying such targets. "Typically, the partner supplies one or more targets, and Medarex works with them to validate the target, develop potential antibody compounds, and select a lead candidate. Together, the partners share development and commercialization costs equally," said Schade.

Rather than partner with one or two genomics companies for access to novel disease targets, as many biotech companies were doing, Medarex made a strategic decision in late 2000 to "play the field" and partner with numerous companies and academic institutions. This approach, Schade explained, has helped Medarex "load up the freezer with a multitude of targets for development of future compounds. Then, it's a matter of selecting the most viable targets, both in terms of biology and patent protection, before moving forward."

At present, Medarex is involved in over 40 such arrangements with other organizations and institutions. As a result, the company has been able to file Investigational New Drug (IND) applications for 3 to 4 compounds annually to pursue the "proof of principle clinical data" it requires to pursue future development. At that point, Schade said, "We decide whether to partner the compound, keep it in house, or drop it from development."

Financial Picture

Another formative event in the company's history was the stock surge that occurred in 2000. "Biotech stocks became the next big thing after the dot-com bust," Schade noted, "and Medarex common stock rose to nearly \$200 per share." The company used this opportunity to raise \$400 million to add to its war chest and fund future development.

In the intervening years, as the biotech sector has fallen in and out of favor, Medarex has



Christian S. Schade,
Senior Vice President and
Chief Financial Officer

used its diverse revenue streams from licensing fees and milestone payments to remain a player in the biotech arena (see Figure 2). It has also been able to draw from its equity

Corporate Philosophy and Challenges

With fewer than 500 employees, Medarex is a tight operation. One key to managing the company's robust pipeline is prioritizing devel-

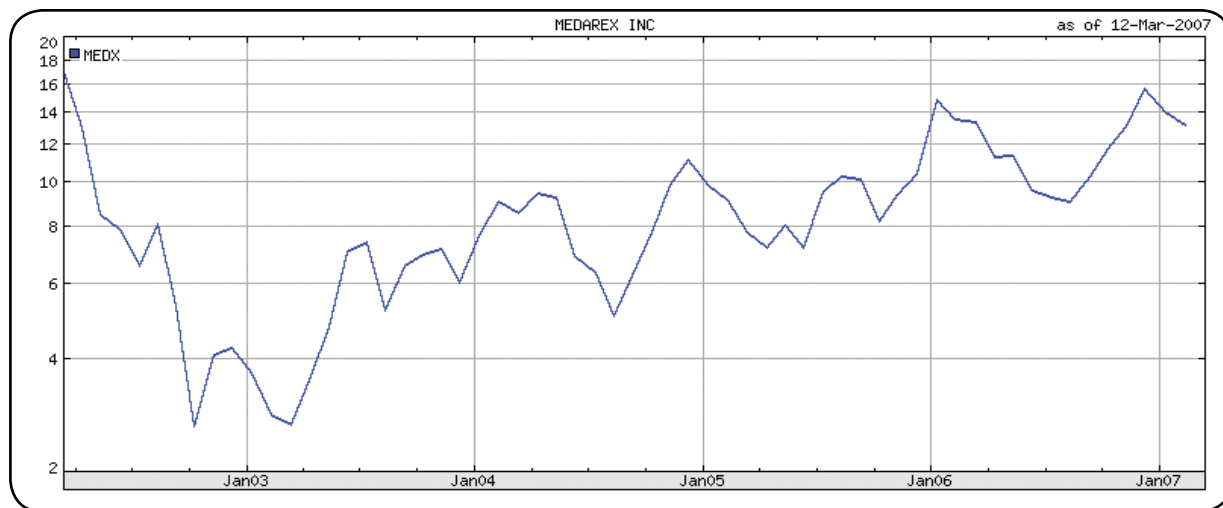


Figure 2: Medarex 5-Year Stock Performance Chart. Source: <http://yahoo.finance.com/>

ownership in Genmab A/S, a Danish company specializing in monoclonal antibodies, which was received as part of a licensing agreement. In February 2007, Medarex took advantage of a surge in Genmab stock, selling off some of its equity to raise \$150 million. Medarex retains approximately 11% equity in Genmab, a stake that remains worth an estimated \$250 to \$300 million.

In March 2007 Medarex reported to investors that it had approximately \$450 million in cash on hand, as well as cash equivalents and marketable securities, approximately \$290 million in equity interests, and an expected operating cash burn of approximately \$13 million per month. Brian Rye, an analyst who has been covering Medarex for Janney Montgomery Scott LLC since 1999, said that this should be enough cash to conduct trials and pay bills comfortably for 2 to 3 years.

opment. “Before moving forward with any compound, we work to secure the patent landscape, make sure the biology is compelling, and then decide how to proceed,” said Schade, who also noted that Medarex has been able to do more with less by “driving efficiencies throughout the organization.” This would include automation of manual tasks, focusing on the cost of goods, conducting right-size clinical trials with cost-per-patient in mind, and adding personnel only where there are bottlenecks in the development process.

The result is a lean, efficient operation with an emphasis on working smart. As Schade pointed out, “this disciplined approach has served us well—our cash burn rate has remained steady during the last 4 years.” **cont. on pg 48 >>**

...Medarex has been able to do more with less ...



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The biggest corporate hurdle Medarex has had to face has been the Securities and Exchange Commission (SEC) investigation in 2006 into the company's historical stock options grant practices. After conducting an investigation of their own, a Special Investigation Committee appointed by Medarex's Board of Directors found irregularities in the company's stock options grant practices and determined that financial results for 2003, 2004, and 2005 had to be restated. As a result of the investigation and the subsequent need for financial restatements, Medarex failed to file timely 10-Q statements during 2006, which earned them a warning from the SEC.

In an effort to correct these irregularities and move forward, the company has pursued a policy of transparency, with full disclosure of past issues and ongoing inquiries, and has put new controls and procedures in place to prevent future irregularities.

In November 2006, the board accepted the resignations of President and Chief Executive Officer Donald L. Drakeman and Chief Financial Officer Michael A. Appelbaum and appointed Irwin Lerner as Interim President and CEO. Previously, Lerner was the Chief Executive Officer and Chairman of the Board of Hoffmann-La Roche Inc. In February 2007, Medarex completed the required restatements, and made their latest 10-K submission on time.

Rye believes that Medarex's responses to the SEC investigation should be sufficient in the eyes of investors. "The Board of Directors has done all the right things to uncover past irregularities and address them, and the company is now current in its filings with the SEC. Perhaps most importantly, the restated numbers did not impact revenue or net cash used in operating activities, nor did they impact income tax expense for any period."

Despite these positive indications, it should be noted that the SEC and US Attorney's office have not yet closed their investigations, and that shareholders may yet move forward with lawsuits alleging breach of fiduciary responsibilities.

Clinical Trials with Ipilimumab

Medarex has high hopes for ipilimumab (MDX-010), an antibody that blocks CTLA-4 (cytotoxic T lymphocyte-associated antigen 4). CTLA-4 is a regulatory molecule found on T-cells that suppresses T-cell activity as part of an apparent feedback mechanism. In a mouse model for prostate cancer, blocking CTLA-4 with ipilimumab was shown to unleash a powerful anticancer immune response. This response was quite specific and distinguished between tumor and non-tumor cells.

Although ipilimumab has shown activity in a variety of cancers, Medarex chose metastatic melanoma as an initial target for clinical development because of the relative ease of measuring objective response, the rapid time-to-progression, and unmet needs for effective therapies. Despite decades of intensive research and development, fewer than 20% of patients with advanced melanoma survive to 5 years.

Three Phase 3 registrational studies are currently underway for ipilimumab. These trials are evaluating ipilimumab in three different strategies for metastatic melanoma:

- As second-line monotherapy in 150 patients with metastatic melanoma, with best objective response rate as the primary endpoint. Enrollment in this study is now complete, and Medarex hopes to report preliminary data and file a Biologic License Application (BLA) for this indication by the end of 2007.
- As first-line therapy with dacarbazine (DTIC) in an expected 500 patients with metastatic melanoma. The primary endpoint is overall progression-free survival.

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...ipilimumab has shown activity in a variety of other solid and liquid tumors.

- As second-line therapy in combination with a therapeutic vaccine, MDX-1379, in a subset of metastatic melanoma patients.

All three trials were initiated under a Special Protocol Assessment (SPA) negotiated with the US Food and Drug Administration (FDA), which outlines definitive clinical objectives and data analyses considered necessary to support regulatory approval. Ipilimumab has received Fast Track designation from the FDA, promising speedy review of Phase 3 data when it is available.

In addition to melanoma, ipilimumab has shown activity in a variety of other solid and liquid tumors. A Phase 3 trial of ipilimumab in prostate cancer is expected to begin in 2007, along with a Phase 2 trial in lung cancer. Phase 2 trials are already underway in renal, breast, and ovarian cancers, as well as lymphoma.

By “lifting the brakes” on T-cell activity, ipilimumab appears to act synergistically with therapeutic cancer vaccines, which are designed to initiate a T-cell response. In addition to an ongoing Phase 3 trial with a melanoma vaccine (MDX-1379), ipilimumab is being studied in combination with GVAX® (Cell Genesys), a whole cell allogeneic vaccine, in hormone-refractory prostate cancer (HRPC). A very small Phase 1 trial showed a greater than 50% reduction in prostate-specific antigen (PSA) for this combination in 5 of 6 patients; 3 of 5 had clinical evidence of antitumor activity that included improvement of bone lesions, resolution of abdominal lymph node disease, and improvement in pain due to bone metastases.

The Bristol-Myers Squibb Partnership

The ambitious clinical trials program for ipilimumab illustrates both the tangible and

intangible benefits of Medarex’s partnership strategy. In 2004, Medarex and BMS inked a collaboration and co-promotion agreement committing to a multi-year \$192 million budget to fund development of ipilimumab, with BMS to pay 65% of development costs in the US and Medarex to pay the remaining 35%.

Medarex is also entitled to regulatory and sales-based payments for regulatory and sales-related milestones, and will have the right to co-promote and receive 45% of profits from US sales. In addition, Medarex received a payment from BMS of \$50 million at signing of the deal, which included an upfront payment of \$25 million and \$25 million for the purchase of Medarex common stock.

Partnering with BMS is about more than just funding: “It provides access to BMS expertise in commercializing oncology products, clinical trials management, and manufacturing,” said Schade.

In return, BMS gets access to a late-stage compound with the potential for broad anti-cancer applications that fits in with their oncology portfolio (e.g., Erbitux® and Sprycel™).

Another anti-CTLA-4 antibody product for melanoma, Pfizer’s CP-675,206, a fully-human antibody product created using Amgen’s Xenomouse® technology, may reach the market in the same timeframe as ipilimumab. But even this cloud has a silver lining for Medarex. Through a license agreement with Pfizer based on the strength of Medarex’s patent position in CTLA-4 antibodies, Medarex is entitled to milestone payments and significant royalties if CP-675,206 is approved. Rye and other analysts feel that the market is large enough for both ipilimumab and CP-675,206, and if either

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agent prevails, Medarex still stands to generate significant revenue.

The Investment Perspective

With the initiation of Phase 3 trials for ipilimumab and ongoing trials for ipilimumab in other tumors—as well as other compounds in various stages of clinical trials and the filing of seven additional INDs—2006 was a busy year for Medarex.

This year looks to be a defining year as well, with the Phase 3 data for ipilimumab and Phase 2 data on several other compounds. Janney Montgomery Scott currently has a “Buy” rating for Medarex, based on commercial prospects for ipilimumab, the versatility of the UltiMAB platform, and the richness of its pipeline. Rye estimated that sales of ipilimumab could reach \$200-300 million in peak annual sales for melanoma alone, with half a billion or more in annual sales possible through off-label use or formal label expansion.

As with any biotech development company, Medarex faces the normal regulatory and commercial hurdles associated with new drug development. By sharing the costs of development, Medarex’s partnerships and alliances tend to help buffer and mitigate these risks. The trade-off is that sharing the risks with its partners and licensees slices into the potential profits Medarex can expect from some of these products. Another inherent risk is that partners and licensees may not have the same sense of urgency as Medarex to move forward with products.

Like most independent biotech companies Medarex may be an attractive acquisition target, particularly for Big Pharma companies with looming expiries and weak pipelines, because of its prolific UltiMAB platform, which is more attractive than ever now that antibodies have established their clinical utility. With so many products in the pipeline, \$250-

300 million equity in Genmab, and a price per share that remains relatively low in the wake of their SEC problems, Medarex might prove a very good buy. Favorable Phase 3 data for ipilimumab would only sweeten the deal.

Future Prospects

Looking ahead, we can expect to start seeing data from Phase 3 trials of ipilimumab in metastatic melanoma, as well as results from earlier-stage trials in other cancers. “One piece of the corporate puzzle that is currently missing is a commercial infrastructure to support the introduction of ipilimumab,” acknowledged Schade. With BLA submission planned for 2007, we can expect to see Medarex begin building this infrastructure with an eye toward future commercialized products as well as ipilimumab. Medarex expects to have approximately 500 to 520 employees by the end of 2007.

The company also plans to initiate Phase 2 studies of MDX-1106, an anti-PD-1 antibody that Medarex is developing in partnership with ONO Pharmaceutical Company, Ltd. The PD-1 molecule is found on the surface of T-cells and appears to “shut down” immune function in response to chronic disease. There is great scientific interest in the role of PD-1 in cancers, human immunodeficiency virus (HIV), and hepatitis C virus (HCV). Furthermore, early studies suggest a potent synergistic effect against tumors when MDX-1106 and ipilimumab are combined at sub-therapeutic doses.

Medarex also anticipates filing at least three new INDs during the coming year, and the formation of additional corporate partnerships.

As royalties begin to accrue from commercialized products, Medarex may decide to keep ownership of a larger portion of their compounds, shouldering more responsibility for development and earning a greater slice of the profits. **DS**

“One piece of the corporate puzzle that is currently missing is a commercial infrastructure to support the introduction of ipilimumab”...

MEDAREX ONCOLOGY PIPELINE

Product Candidate/Target	Indication	Clinical Status	Partner/Nature of Agreement
MDX-010 (ipilimumab) anti-CTLA-4	melanoma, other cancers	Phase 3	Bristol-Myers Squibb Co-promote/Profit share
HuMax-CD4 (zanolimumab) anti-CD4	cutaneous T-cell lymphoma	Phase 3	Genmab/Merck Serono Equity interest
HuMax-CD20 (ofatumumab) anti-CD20	lymphomas	Phase 3	Genmab Equity interest
HuMax-EGFR (zalutumumab) anti-EGFR	head and neck cancer	Phase 3	Genmab Equity interest
MDX-060 anti-CD30	Hodgkin's disease, anaplastic large cell lymphoma	Phase 2	Wholly-owned
CNTO 95 anti-integrin receptors	Cancer	Phase 1/2	Centocor Milestones/Royalties
MDX-1307 anti-Mannose receptor/hc8B	Cancer	Phase 1	Celldex Equity interest
MDX-1106 (ONO-4538) anti-PD1	Cancer	Phase 1	ONO Pharmaceutical Co-development
HGS-TR2J anti-TRAIL-R2	Cancer	Phase 1	Kirin Technology Royalties
BMS-66513 cancer	Cancer	Phase 1	Bristol-Myers Squibb Milestones/Royalties
IMC-3G3 anti-PDGFRa	Cancer	Phase 1	ImClone Systems Milestones/Royalties
MDX-1401 anti-CD30	Cancer	Phase 1	Wholly-owned

Contact:

Medarex, Inc., Corporate Office

707 State Road, Princeton, NJ 08540-1437

Tel: (609) 430-2880 Email: information@medarex.com



Unsung Heroes—Vaccine Adjuvants and Co-Stimulators

A successful therapeutic cancer vaccine must evoke a robust T-cell response directed at a cancer-specific antigen. In the latest generation of therapeutic cancer vaccines, researchers are turning to adjuvants and co-stimulators to direct and magnify T-cell response. Because they can be used in

or alongside vaccines directed at a variety of cancers, adjuvants and co-stimulators may have broad uses and applications.

The table below presents a sampling of adjuvants and co-stimulators in various stages of development.

UNsung HEROES—VACCINE ADJUVANTS AND CO-STIMULATORS

Compound	How It Works	Examples of Use with Vaccines
GM-CSF (Leukine®; sargramostim, Berlex)	<p>Stimulates proliferation and function of antigen-presenting cells, encouraging them to present the cancer-associated antigen to T-cells</p> <p>Also being studied alone or in combination with chemotherapy for some cancers</p> <p>Already licensed to boost neutrophil production following bone marrow transplantation and after chemotherapy for certain cancers</p>	<p>Clinical trials in B-cell lymphoma in conjunction with FavID® (Faville), MyVax® (Genitope), and BiovaxID™ (Biovest)</p> <p>Used in the production of GVAX® and Provenge®, which are in Phase 3 development for prostate cancer</p>
Ipilimumab (MDX-010; Medarex)	<p>Blocks CTLA-4, a regulatory molecule that suppresses T-cell response; may work synergistically with vaccines</p> <p>Also being studied alone or in combination with chemotherapy for some cancers</p>	<p>Being studied in clinical trials in conjunction with: MDX-1379 for metastatic melanoma</p> <p>GVAX for prostate cancer</p>
Vaximmune™ (Coley)	<p>Stimulates TLR9 (toll-like receptor 9), a receptor found on the surfaces of dendritic cells. TLR9 helps the immune system recognize the DNA of invading pathogens</p> <p>When used with therapeutic cancer vaccines, may increase antibody and cytotoxic T-cell responses against vaccine antigens</p> <p>Also being studied in other vaccine types</p>	<p>Incorporated into cancer vaccine products being developed by GSK and Novartis Vaccines & Diagnostics</p>
QS-21 Stimulon® (Antigenics)	<p>Stimulates T-cell responses, including Th1 and Th2 cells and cytotoxic T-cells; also boosts antibody response</p> <p>When used with therapeutic cancer vaccines, may enhance antigen presentation and increase cytotoxic T-cell responses against vaccine antigens</p> <p>Also being studied in other vaccine types</p>	<p>Incorporated into cancer vaccine products being developed by GSK, Progenics, and Pharmexa for a variety of cancers (e.g., melanoma, breast, lung, colorectal, and pancreatic)</p>

>> OBR DAILY NEWS FLASH

British biotech Oxford Bio-Medica signed a \$690 million deal for its flagship product TroVax(R) with Sanofi-Aventis signalling growing confidence in the emerging field of cancer vaccines among Big Pharma; Sanofi plans to immediately launch new studies of TroVax in colorectal cancer. (Reuters.com, 3/28/07)

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medical communications, clearly.

