Maxygen Inc.

ChemE 450 Term Paper

Table of Contents

Overview
Company Background
Maxygen's Founders5
Alejandro Zaffaroni, Ph.D
Russell Howard, Ph.D., Chief Executive Officer
Willem "Pim" Stemmer, Ph.D., former Vice President of Research
Isaac Stein, J.D., M.B.A., Chairman of the Board of Directors
Technology Platform6
Product Pipeline
Interferon Beta
Interferon Gamma 9
Interferon Alpha
Myelosuppression Treatment
Conclusion11
Exhibits
Exhibit 1: Schematic of the Molecular Breeding Cycle
Exhibit 2: Maxygen's Key Patents
Exhibit 3: Product Pipelines
Codexis' Product Pipeline
Verdia's Product Pipeline
Maxygen's Product Pipeline
References Cited
Other References

Overview

Maxygen, Inc. is a leading company in the field of applied biotechnology. The company has specific expertise in the development and application of proprietary directed molecular evolution technologies, also known as "Molecular BreedingTM" technologies, and other complementary technologies to evolve new or improved properties into single genes, multigene pathways, vectors, and genomes. Maxygen's proprietary and broad genetic technology appears to be capable of rapidly producing proteins with improved performance characteristics to be used as industrial enzymes, drug candidates, and crop enhancers. Maxygen's proprietary science creates a strong technology platform with broad applicability across many industry sectors. Maxygen is focused on using its technology to develop therapeutic proteins to be used as drug candidates. Maxygen also owns two industrial businesses, Codexis and Verdia, which use Molecular Breeding technology to develop industrial chemical enzymes and crop enhancers, respectively. In the development of human therapeutics, Maxygen is focused on developing protein pharmaceuticals, prophylactic vaccines, and therapeutic vaccines for multiple forms of cancer; infectious diseases, including HIV, hematology, allergies; and autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis. The chemicals segment, Codexis, develops biocatalytic processes, particularly proprietary catalysts and processes for the production of pharmaceutical products. The agriculture segment, Verdia, provides proprietary product solutions for commercial problems in plant-based businesses through the application of DNA breeding methods. Maxygen is headquartered in Redwood City, CA. They employ nearly 300 people. The company competes with Eli Lilly, Pharmacia, Genentech, Amgen, Human Genome Sciences, Corixa Corp., Vical Corp., GlaxoSmithKline, Merck, Dow Chemical, Genencor, Diversa Corp., Monsanto, DowAgroScience, and Paradigm Genetics.

Company Background

In 1994, Dr. Willem "Pim" Stemmer, a scientist at Affymax, developed a PCR technique to create new, diverse mutant genes by randomly shuffling DNA from several mutant gene sources (1). Later research showed that DNA shuffling techniques could be used to direct the evolution of genes, combining useful mutations from individual genes to achieve significant improvements in gene performance (2). This research suggested that DNA shuffling techniques

would allow the creation of novel properties within any protein, pathway, or vector through the evolution of its DNA sequence. Dr. Stemmer's research is the basis for Maxygen's Molecular Breeding technology.

At the time, Affymax was a wholly owned subsidiary of Glaxo Wellcome. Glaxo agreed to spin-out the technology and form a separate company in order to ensure that the technology would be aggressively developed and commercialized in diverse areas.

Maxygen, Inc. was founded in 1997 with a group headed by Dr. Alejandro Zaffaroni, a leading biotech entrepreneur in the San Francisco Bay Area. In a press release, Dr. Zaffaroni stated:

"DNA shuffling is a fundamentally new technology which has tremendous potential in numerous areas of commercial value. Formation of Maxygen as an independent company will allow us explore new areas where the technology has maximal value and invest our resources accordingly. I believe the technology can be used to rapidly develop new human therapeutics that are based on novel DNA sequences." (3)

Dr. Zaffaroni's group included key talent taken from Affymax. Dr. Stemmer became Maxygen's Vice President of Research. Dr. Russell Howard left his position as President and Scientific Director of Affymax to join Maxygen as President and Chief Operating Officer. Another key founder of the company is Isaac Stein, who serves as Maxygen's Chairman of the Board of Directors. The founders are profiled below.

Maxygen was created with the goal of becoming a drug development leader by using their Molecular Breeding technology to evolve novel proteins, pathways, and vectors. Since the technology can be applied to a wide range of genetic targets, including single genes, multi-gene pathways, plasmids, and viral genomes, the company explored commercial opportunities for the controlled evolution of novel industrial enzymes and metabolic processes, novel products in the agricultural industry, as well as opportunities in human medicine.

The company met with early success. By January 1999, it had formed partnerships with Novozymes, Pfizer, and DuPont, in the areas of industrial enzymes, therapeutic proteins, and

-

¹ Glaxo Wellcome merged with SmithKlein Beecham to become GlaxoSmithKlein. Affymax was spun off as an independent company during the merger. GSK has retained 23% ownership of Affymax.

agricultural development, respectively. These partnerships generally involved upfront payments to Maxygen, funding of Maxygen's R&D efforts, and milestone payments based upon meeting certain development and commercialization targets. According to Maxygen's President, Dr. Simba Gill, Maxygen's board wanted the company to stay focused on the area of therapeutic proteins, so they spun-off two new companies which would use Maxygen's Molecular Breeding technology and apply it to areas outside of human therapeutics (4). These companies were Codexis and Verdia, which develop industrial enzymes and agricultural products, respectively.

Maxygen's Founders

Alejandro Zaffaroni, Ph.D.

Dr. Zaffaroni is a leading San Francisco Bay Area scientist and entrepreneur. He is known for being able to recognize the commercial value in leading-edge technologies and has founded several companies based around specific technology platforms. Dr. Zaffaroni received his B.Sc. from the University of Montevideo, Uruguay in 1941, and his Ph.D. in biochemistry from the University of Rochester in 1949. He joined Syntex Laboratories in 1951 and helped that company as they pioneered the development of the birth control pill. Eventually he was appointed President of Syntex. In 1968, he resigned from Syntex to found Alza Corp. This company was founded on the idea of improving medical treatment through controlled drug delivery. Alza has since become the industry leader in drug-delivery technology. In 1980, Dr. Zaffaroni began a long streak developing successful companies, including: DNAX Ltd. (1980), Affymax (1989), Affymetrix (1991), Symyx (1994), Maxygen (1997), SurroMed (1998), and Alexza MDC (2000). His activity in the healthcare industry over the past fifty years has allowed Dr. Zaffaroni to build a vast network of acquaintances that have been instrumental in allowing him to successfully startup companies like Maxygen. "It is not many entrepreneurs who can call up half a dozen close friends who happen to be Nobel-prize winning scientists, and get them to invest their cash and expertise in a venture (5)."

Russell Howard, Ph.D., Chief Executive Officer

Dr. Howard is a leading scientist in the biotechnology industry. He has over 140 publications in peer-reviewed journals in addition to numerous patents. Dr. Howard received his Ph.D. in biochemistry from Melbourne University, Australia. Dr. Howard held various research

position at DNAX Research Institute and the National Institute of Health before joining Affymax in 1994, where he served as President and Scientific Director. In 1997 he helped co-found Maxygen, and has served as the company's CEO since then. He was appointed to Maxygen's Board of Directors in 1998.

Willem "Pim" Stemmer, Ph.D., former Vice President of Research

Dr. Stemmer is the inventor of DNA breeding technology. He has authored more than 60 research publications and is the inventor on more than 70 issued patents and has more than 150 pending applications. Dr. Stemmer obtained his Ph.D. from the University of Wisconsin at Madison in 1985 on bacterial virulence mechanisms. In 1985, Dr. Stemmer founded Genetic Designs, Inc. Dr. Stemmer joined Hybritech Inc. in 1987, where he worked as a research scientist on antibody fragment engineering in *E.coli* and mammalian cells for use in cancer therapy. In 1993, Dr. Stemmer invented and developed DNA shuffling technology as a Distinguished Scientist at Affymax. With the help of Dr. Zaffaroni, he co-founded Maxygen to develop his DNA shuffling technology into a commercial product. Dr. Stemmer left Maxygen in 2003 to found Avidia, Inc., which is focused on directed evolution of antibody-like products.

Isaac Stein, J.D., M.B.A., Chairman of the Board of Directors

Mr. Stein received his J.D. and M.B.A. from Stanford University. Since 1982, Mr. Stein has been president of Waverly Associates, Inc., a private investment firm. Mr. Stein is also a managing member of Technogen Enterprises. He is Chairman of the Board of the Trustees of Stanford University, and director of several privately held companies including Surromed Corporation and Stony Hill Vineyard and is a member of the International Advisory Board of the Singapore EDB. He previously served as a director of Alza Corp., Raychem Corp., Symyx, and CV Therapeutics, among other public companies, and as Chairman of UCSF/Stanford Health Care.

Technology Platform

Based on research preformed by Dr. Stemmer (1, 2), Maxygen has commercialized his DNA shuffling techniques into their "Molecular Breeding" technology (see Exhibit 1). This technology is proprietary and relies on several key patents, including US Patent No. 5,605,793, "Methods for In Vitro Recombination" and US Patent No. 5,811,238, "Methods for Generating

Polynucleotides Having Desired Characteristics by Iterative Selection and Recombination." See Exhibit 2 for a list of Maxygen's key patents.

Maxygen's Molecular Breeding technologies work as follows (6): a single gene or multiple related genes are cleaved into fragments and recombined creating a population of novel gene sequences. The novel genes created by Molecular Breeding are then selected for one or more desired characteristics. This selection process yields a population of genes which becomes the starting point for the next cycle of recombination. As with classical breeding, this process is repeated until genes expressing the desired properties are identified. Molecular Breeding can be used to evolve properties which are coded for by single genes, multiple gene pathways, and entire genomes. By repeating the process, Molecular Breeding can ultimately generate libraries with a high percentage of functional genes. Due to the high quality of these libraries, only a relatively small number of assays need to be performed in order to identify gene variants with the desired commercial qualities. This process can significantly reduce the cost and time associated with identifying multiple product candidates.

Next, the gene library is screened using Maxygen's proprietary MaxyScanTM screening system. The ability to screen or select for a desired improvement in gene function is essential to the effective development of a gene or protein with the desired property (6). As a result, Maxygen has invested significant resources in developing automated, rapid screening and selection systems. Maxygen has developed flexible screening systems which measure the production of small molecules in cultures without significant purification steps or specific assay reagents, thereby eliminating two time-consuming steps required for traditional screening. Maxygen has also developed reliable, cell-based screens that are predictive of specific functions. Maxygen continues to develop new screening approaches and technologies to accelerate the identification of desired improvements. Maxygen's uses a multi-tiered screening system, whereby a less sensitive screen is used to rapidly select gene products with the desired characteristics, followed by a more sensitive screen to confirm value in these variants and to select for final lead product candidates. Unlike alternative approaches which create random diversity, Molecular Breeding can produce high-quality libraries with both genetic diversity and a predominance of active functional genes. This allows Maxygen to use complex biological screens and formats as a final test, as relatively few gene products must be screened in order to detect an improvement in the starting gene activity.

Product Pipeline

Maxygen has a robust product pipeline in all of its research areas. See Exhibit 3 for a complete list of products in development by Codexis, Verdia, and Maxygen. Codexis is currently the most successful of the business units, with five commercialized products. Codexis is a profitable business unit, and these profits are used to offset the losses incurred by its parent company. Verdia has several products which may soon enter commercialization. The focus of this section will be on Maxygen's pipeline for human therapeutics.

Maxygen is trying to shorten the drug discovery process by focusing their efforts on developing superior versions of existing drugs (7). Maxygen uses information about genes and proteins obtained from the vast data in the public domain about validated commercial targets. Once a potential optimization candidate is identified, the company then considers if and whom to partner with on the project. Maxygen receives much of its business from partnerships with large bio/pharma companies. These companies hire Maxygen to optimize commercialized drugs by using their Molecular Breeding technology. Maxygen currently has four primary therapeutic proteins in development. These products are detailed below:

Interferon Beta

Interferon beta is used in the treatment of multiple sclerosis (MS). MS affects 400,000 Americans and 2.5 million people worldwide. The estimated worldwide market for interferon beta is currently \$2 billion, and is expected to grow to \$3 billion within the next 5 to 10 years. Clinical data suggests that interferon beta may also be useful in treating cancer, infectious diseases, and autoimmune diseases.

Multiple sclerosis is a chronic autoimmune disease of the central nervous system. Patients have abnormal immune responses which damage the myelin-covered sheaths that insulate nerve fibers in the brain and spinal cord. MS can be a debilitating disease. Symptoms included loss of muscle strength and extreme fatigue. In severe MS, patients have partial or complete paralysis on a permanent basis.

Interferon beta is a naturally occurring protein in the human body that has multiple effects on the immune system. The protein increases the activity of suppressor lymphocytes and inhibits stimulation of other immune cells. These effects are thought to reduce the immune

response responsible for myelin damage in people with MS, thereby slowing progression of the disease. The FDA has approved three interferon beta medications.

In September 2000, Maxygen entered into a partnership with H. Lundbeck A/S to research and develop a protein pharmaceutical product which could be used for central nervous system diseases, including MS. Maxygen developed an optimized form of interferon beta (MAXY 10) which, when compared to existing interferon beta treatments, had improved pharmacokinetics, pharmacodynamics, selectivity, and affinity, as well as reduced protein immunogenicity. Maxygen's beta interferon was engineered to have a substantially improved half-life, which should reduce the dosing frequency from every second day, as with current treatments, to once every seven to ten days. In February 2002, Lundbeck and Maxygen announced that Lundbeck would move Maxygen's interferon beta forward into human clinical trials. In late 2003, Maxygen ended their partnership with Lundbeck and repurchased the marketing rights to their interferon beta candidate. Maxygen is currently completing pre-clinical studies on interferon beta and is expected to make an Investigational New Drug (IND) filing in 2005.

Interferon Gamma

Interferon gamma is used in the treatment of idiopathic pulmonary fibrosis (IPF). IPF affects 75,000 Americans, and an approximately 15,000 new cases develop each year. The estimated worldwide market for interferon gamma is \$2 billion. Interferon gamma may have broad applicability to other lung diseases such as cystic fibrosis, certain infectious diseases such as cryptococcal meningitis, as well as ovarian cancer and lymphoma.

Idiopathic pulmonary fibrosis is an inflammatory disease that results in scarring of the lungs. IPF hinders the patient's ability to breath, causing shortness of breath and coughing. IPF is a progressive disease, and symptoms increase in severity over time. The disease is disabling and can be fatal. Currently there are no drugs approved by the FDA for the treatment of IPF.

Interferon gamma is a naturally occurring protein in the human body that plays a role in the activation of the immune system against infectious pathogens. The protein is believed to prevent the excessive scarring in the lungs associated with IPF. InterMune currently markets an interferon gamma medication, Actimmune, for the treatment of chronic granulomatous and malignant osteopetrosis. Actimmune is in late-stage clinical trials for the treatment of IPF.

In September 2001, Maxygen and InterMune entered into a licensing and collaboration agreement to develop and commercialize a novel, next-generation interferon gamma product (8). Under the terms of the agreement, InterMune will take product candidates created by Maxygen into clinical development. InterMune is funding Maxygen's R&D efforts in developing a next-generation interferon gamma product while InterMune has retained exclusive commercialization rights on successful product candidates. Maxygen has received up-front licensing fees and full research funding and will receive development and commercialization payments which could exceed \$60 million. Maxygen currently has one candidate, MAXY 50, in pre-clinical development. MAXY 50 has shown improved pharmacokinetic properties that may allow reduced dosing as well as improved efficacy compared with Actimmune. Maxygen hopes to file an IND for MAXY 50 in 2005.

Interferon Alpha

Interferon alpha is used in the treatment of hepatitic C virus (HCV). The World Health Organization estimates that HCV affects 170 million people, or 3% of the world population. In the United States, there are thought to be 2.7 million people with chronic HCV infections.

Hepatitis C virus is a contagious viral infection that can lead to serious liver disease. No vaccine exists to prevent infection. Over time, the infection may lead to long-term liver disease, including hepatitis, cirrhosis, and cancer. Liver transplantation may be lifesaving in end-stage liver disease, but for HCV-positive patients, reinfection is almost universal.

Interferon alpha is a naturally occurring protein in the body with broad antiviral and antiproliferative effects. Recombinant versions of interferon alpha are approved to treat HBV, HCV, and several forms of cancer.

In May 2003, Roche and Maxygen formed a broad strategic alliance to collaborate on the development of next-generation interferon alpha variants for commercialization. Analysts estimate this deal to be valued at \$230 million, excluding possible royalty payment if the product is successfully commercialized (9). Maxygen has used its proprietary technologies to develop multiple optimized versions of interferon alpha that are designed to have superior safety and efficacy profiles compared to other interferon alpha products currently on the market. The improved interferon alphas have been engineered to induce enhanced antiviral activity and

immune response to clear the virus more effectively in patients who do not respond to existing therapies. This product is in pre-clinical development.

Myelosuppression Treatment

Myelosuppression affects 2 million people worldwide. The current market value for the treatment of this disease is \$8 billion. Myelosuppression is the decreased production of important components of the blood, including red blood cells, platelets, and some white blood cells. Myelosuppression is a common side effect of chemotherapy treatments for many forms of cancer, including breast cancer, lung cancer, lymphoma, and leukemia. Myelosuppression puts the patient at significant risk of suffering from disorders, including anemia, thrombocytopenia, or neutropenia. Myelosuppression can result in the reduction of dosing or delay of treatment for patients undergoing chemotherapy, which may decrease the overall efficacy of chemotherapeutic treatments.

Recombinant versions of cytokines are used to treat myelosuppression. Cytokines are naturally occurring proteins found in the body that are produced by the cells to effect basic functions of the immune system. Erythropoietin (EPO), granulocyte macrophage-colony stimulating factor (GMCSF), and granulocyte-colony stimulating factor (G-CSF) are three FDA-approved cytokine drugs used to decrease the duration of myelosuppression and prevent complications that arise from reduced levels of red blood cells or white blood cells (7). Currently, EPO dominates the market for the treatment of anemia, while G-CSF is used for the treatment of neutropenia.

Maxygen has developed a cytokine variant (MAXY 996) for the treatment of myelosuppression. Current cytokine therapies have poor pharmacokinetic performance. This product is in pre-clinical development and Maxygen has not yet found a partner to help develop MAXY 996. Maxygen says that an IND could be filed in 2005 while analysts believe the product will not be ready for an IND filling until 2006 (7, 9).

Conclusion

Maxygen is an innovative biotechnology with a strong product pipeline and enough cash on hand to fund their research efforts for several more years. Their proprietary technology, combined with an excellent executive team, has allowed Maxygen to be very successful for a

biotechnology company that was founded only seven years ago. Maxygen's near-term profitability relies on the success of its subsidiaries (Codexis and Verdia) and the signing of additional therapeutic alliances. The company's long-term success relies on the continued development of lead therapeutics by its partners (Roche and InterMune) and the partnering of internal therapeutic programs (9).

Exhibits

Exhibit 1: Schematic of the Molecular Breeding Cycle

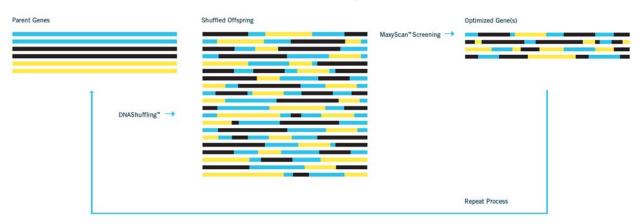


Exhibit 2: Maxygen's Key Patents

US Patent		
No.	Title	Date
6,399,383	Human Papilloma Virus Vectors	4-Jun-2002
6,395,547	Methods for Generating Polynucleotides Having Desired Characteristics by Iterative Selection and Recombination	28-May-2002
6,391,640	Methods and Compositions for Cellular and Metabolic Engineering	21-May-2002
6,391,552	Enhancing Transfection Efficiency of Vectors by Recursive Recombination	21-May-2002
6,387,702	Enhancing Cell Competence by Recursive Sequence Combination	14-May-2002
6,379,964	Evolution of Whole Cells and Organisms by Recursive Sequence Recombination	30-Apr-2002
6,376,246	Oligonucleotide Mediated Nucleic Acid Recombination	23-Apr-2002
6,372,497	Methods for Generating Polynucleotides Having Desired Characteristics by Iterative Selection and Recombination	16-Apr-2002
6,368,861	Oligonucleotide Mediated Nucleic Acid Recombination	9-Apr-2002
6,365,408	Methods of Evolving a Polynucleotides by Mutagenesis and Recombination	2-Apr-2002
6,365,377	Recombination of Insertion Modified Nucleic Acids	2-Apr-2002
6,358,740	Recombination of Insertion Modified Nucleic Acids	19-Mar-2002
6,358,742	Evolving Conjugative Transfer of DNA by Recursive Recombination	19-Mar-2002
6,355,484	Methods and Compositions for Polypeptides Engineering	12-Mar-2002
6,352,859	Evolution of Whole Cells and Organisms by Recursive Sequence Combination	5-Mar-2002
6,344,356	Methods for Recombining Nucleic Acids	5-Feb-2002
6,337,186	Method for Producing Polynucleotides with Desired Properties	8-Jan-2002
6,335,160	Methods and Compositions for Polypeptide Engineering	1-Jan-2002
6,335,198	Evolution of Whole Cells and Organisms by Recursive Sequence Recombination	1-Jan-2002
6,326,204	Evolution of Whole Cells and Organisms by Recursive Sequence Recombination	4-Dec-2002

	Methods for Generating Polynucleotides Having Desired Characteristics by	
6,323,030	Iterative Selection and Recombination	27-Nov-2001
6,319,714	Oligonucleotide Mediated Nucleic Acid Recombination	20-Nov-2001
6,319,713	Methods and Compositions for Polypeptide Engineering	20-Nov-2001
6,309,883	Methods and Compositions for Cellular and Metabolic Engineering	30-Oct-2001
6,303,344	Methods and Compositions for Polypeptide Engineering	16-Oct-2001
6,297,053	Methods for Generating Polynucleotides Having Desired Characteristics by Iterative Selection and Recombination	2-Oct-2001
6,291,242	Methods for Generating Polynucleotides Having Desired Characteristics by Iterative Selection and Recombination	18-Sep-2001
6,287,861	Methods for Generating Polynucleotides Having Desired Characteristics by Iterative Selection and Recombination	11-Sep-2001
6,287,862	Evolution of Whole Cells and Organisms by Recursive Sequence Recombination	11-Sep-2001
6,277,638	Methods for Generating Polynucleotides Having Desired Characteristics by Iterative Selection and Recombination	21-Aug-2001
6,265,201	DNA Molecules and Protein Displaying Improved Triazine Compound Degrading Ability	24-Jul-2001
6,251,674	Evolution of Whole Cells and Organisms by Recursive Sequence Recombination	26-Jun-2001
6,180,406	Methods for Generating Polynucleotides Having Desired Characteristics by Iterative Selection and Recombination	30-Jan-2001
6,165,793	Methods for Generating Polynucleotides Having Desired Characteristics by Iterative Selection and Recombination	26-Dec-2000
6,132,970	Methods of Shuffling Polynucleotides	17-Oct-2000
6,117,679	Methods for Generating Polynucleotides Having Desired Characteristics by Iterative Selection and Recombination	12-Sep-2000
6,096,548	Method for Directing Evolution of a Virus	1-Aug-2000
5,837,458	Methods and Compositions for Cellular and Metabolic Engineering	17-Nov-1998
5,834,252	End-Complementary Polymerase Reaction	10-Nov-1998
5,830,721	DNA Mutation by Random Fragmentation and Reassembly	3-Nov-1998
5,811,238	Methods for Generating Polynucleotides Having Desired Characteristics by Iterative Selection and Recombination	22-Sep-1998
5,605,793	Methods for In Vitro Recombination	25-Feb-1997

Exhibit 3: Product Pipelines

Source: Ref. 9.

Codexis' Product Pipeline

Product description	Parnter	Pre- Development	Development	Commercial
Enzymes for pharma. manufacturing	Pfizer	x	X	x
Enzymes for penicillin production	DSM	X	Х	х
Enzyme for food processing	Novozymes	Х	Х	Х
Enzyme for pulp and paper	Novozymes	X	X	X
Enzyme for laundry detergents	Novozymes	X	X	X
Industrial enzymes	Novozymes	X	X	

Industrial enzymes	Novozymes	х	X	
Industrial enzymes	Novozymes	Х	Х	
Enzymes for increasing CO2 fixation	Rio Tinto	х		
Biosynthesis of petrochemicals (methanol)	Chevron	x		
Biocatalysts for pulp and paper	Unpartnered	х		
Biosynthesis of lactic acid for fibers	Cargill Dow	x		
Improved fermentation for natural products production	Eli Lilly	Х		
API by fermentation (generic)	Sandoz	Х		

Verdia's Product Pipeline

Product description	Parnter	Pre- Development	Crop Development	Commercial
Crop protection and improved traits	DuPont/ Pioneer Hi- Bred	X (> =1)	X (4)	
(corn, soybean) Crop yield and protection, others	Verdia	X (> =8)		
Crop yield and quality	Syngenta	X (> =2)	X (2)	
Crop protection (cotton)	Delta and Pine Land	X (> =2)	X (1)	

Maxygen's Product Pipeline

Compound	Molecule	Indication	Parnter or Maxygen	Creation	Screen/ Optimize	Lead candidate	Pre- clinical
Maxy 10	Interferon beta	CNS and MS	Maxygen	Х	Х	Х	Х
Maxy 50	Interferon gamma	IPF	Intermune	х	х	х	х
Maxy 996	cytokine	Myelosup-pression	Maxygen	X	X	X	Χ
Maxy 1200 (a)	DNA vaccine	Colorectal cancer	Maxygen	Х	Х	х	х
Maxy 1500 (a)	DNA vaccine	Dengue	Maxygen	x	x	х	х
Maxy 24	Interferon alpha	Hepatitis B Hepatitis C	Roche	х	х	х	
Maxy 1100	DNA vaccine	Hepatitis B	Maxygen	Х	Х	X	
Maxy 30		Autoimmune	Maxygen	Χ	Χ	X	
Maxy 912		Cancer	Maxygen	Χ	X	X	
Maxy 968		Hemostasis	Maxygen	Χ	X		
Maxy 201		HIV	Maxygen/ IAVI	Χ	Χ		
Maxy 914		Cancer	Maxygen	X	Х		
Maxy 14		Cancer	Maxygen	Χ	Χ		
Maxy 318		Hemostasis	Maxygen	Χ	Χ		
Maxy 20		Allergy	ALK-Abello	Х	Х		
Maxy 320		Allergy	ALK-Abello	Х	Х		
Maxy 735		Autoimmune	Maxygen	Χ	Χ		
Maxy 635		Undisclosed	Aventis	Х	Х		
Maxy 58		Metabolic disease	Maxygen	Χ	Χ		
Maxy 678		Malaria	Maxygen/USAID	Х	Х		
NA	Anti-bodies	Undisclosed	CellTech		X		
Maxy 740		Inflammation	Maxygen	Х	_	_	
Maxy 829		Equine encephalitis	Maxygen/ USAMRMC	х			

References Cited

- Stemmer, W. P. C., "DNA Shuffling by Random Fragmentation and Reassembly: In vitro Recombination for Molecular Evolution." <u>Proceedings of the National Academy of</u> <u>Sciences</u>, Vol. 91, No. 22 (1994): p. 10747-10751.
- 2) Crameri, A., et al. "DNA shuffling of a family of genes from diverse species accelerates directed evolution." Nature, Vol. 391 (1998): p. 288-291
- 3) <u>Maxygen Press Releases</u>. June 2, 1997. Maxygen, Inc. Accessed May 22, 2004. <u>www.maxygen.com</u>.
- 4) Interview with Simba Gill, M.B.A., Ph.D., President of Maxygen. March 17, 2004. Redwood City, CA.
- 5) "Biotech's Father William." The Economist. June 24, 1999.
- 6) Maxygen, Inc. 1999 Annual Report.
- 7) Maxygen, Inc. 2002 Annual Report.
- 8) Life Science Analytics, Inc. Maxygen Deals & Alliances. February 3, 2004.
- 9) J.P. Morgan North American Equity Research. <u>Genomic/Life Sciences Review.</u> April 16, 2004.

Other References

- 1) Welcome to Maxygen. Maxygen, Inc. Accessed May 22, 2004. http://www.maxygen.com/indexa.php.
- 2) Emed Securities, Inc. Maxygen Extended Pipeline Report. January 7, 2004.
- 3) Life Science Analytics, Inc. Maxygen Pipeline Report. February 3, 2004.
- 4) Life Science Analytics, Inc. Maxygen Financial Report. January 30, 2004.
- 5) USB Warburg Global Equity Research. Maxygen, Inc. Analyst Report. May 29, 2002.
- 6) J.P. Morgan North American Equity Research. <u>Maxygen, Inc.: Lundbeck Partnership</u>
 <u>Ends</u>. October 29, 2003.
- 7) J.P. Morgan North American Equity Research. <u>Maxygen, Inc.: MAXY Advances</u>

 <u>Therapeutic Proteins at a Cost.</u> February 2, 2004.

- 8) "Maxygen 1Q EPS Loss 29c vs. 12c." The Wall Street Journal. April 27, 2004.
- 9) "Sex in a Bottle." The Economist. June 24, 1999.
- 10) Stemmer, W., Holland, B., "Survival of the Fittest Molecule." <u>American Scientist</u>. Vol. 91 (2003): p. 526-533.