生物工程技术和生物工程产业的发展

Biotechnology and Bio-industry Development

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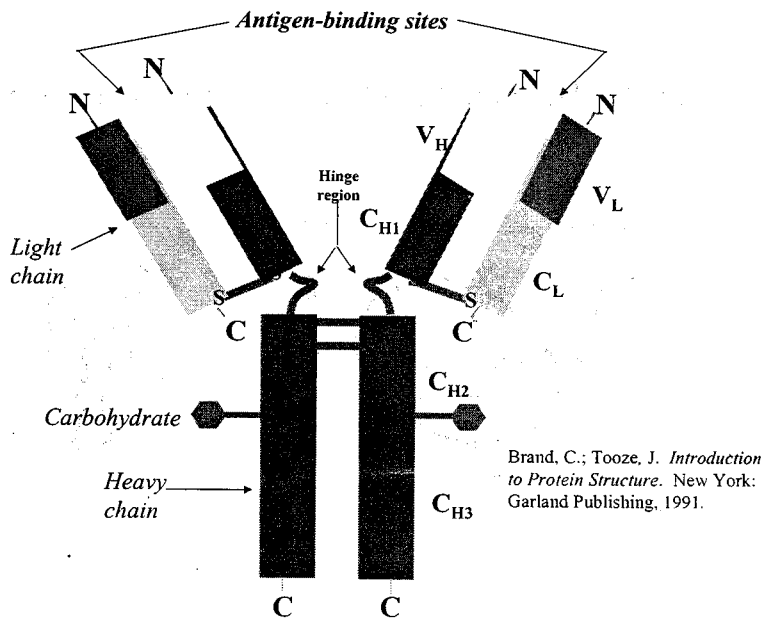
MEDAREX



Brand, C.; Tooze, J. *Introduction to Protein Structure.* New York: Garland Publishing, 1991.

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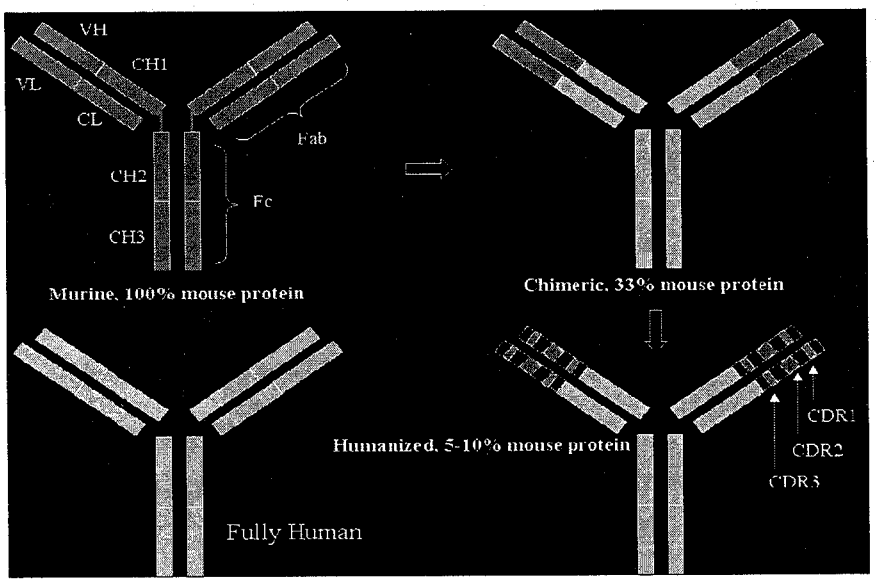
Therapeutic Antibody Development



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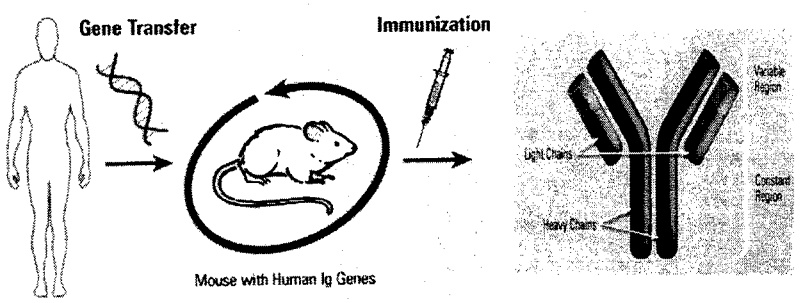
UltiMAb Human Antibody Development System®



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US FDA Approved Therapeutically Monoclonal Antibodies

JM Reichert. CJ Rosensweig. LB Faden & MC Dewitz. Monoclonal Antibody Success in Clinic. *Nat Biotechnol.*2005: 23. 1073-1078.

Table 1 US and EU therapeutic mAb approvals to date

Generic	Company/location	Trade	Description	Therapeutic category	Approval date
Muromonab-CD3	Johnson & Johnson New Brunswick, New Jersey	Orthoclone OKT3	Murine, IgG2a, anti-CD3	Immunological	06/19/86 (US)
Abciximab	Centocor	ReoPro	Chimeric, IgG1, anti-GPIIb/IIIa; Fab	Hemostasis	12/22/94 (US)
Rituximab	Genentech	Rituxan	Chimeric, IgG1κ, anti-CD20	Oncological	11/26/97 (US) 06/02/98 (EU)
Daclizumab	Hoffmann-La Roche Basel	Zenapax	Humanized, IgG1κ, anti-CD25	Immunological	12/10/97 (US) 02/26/99 (EU)
Basiliximab	Novartis Basel	Simulect	Chimeric, IgG1κ, anti-CD25	Immunological	05/12/98 (US) 10/09/98 (EU)
Palivizumab	MedImmune Gaithersburg, Maryland	Synagis	Humanized, IgG1κ, anti-respiratory syncytial virus	Anti-infective	06/19/98 (US) 08/13/99 (EU)
Infliximab	Centocor	Remicade	Chimeric, IgG1κ, anti-tumor necrosis factor (TNFα)	Immunological	08/24/98 (US) 08/13/99 (EU)
Trastuzumab	Genentech	Herceptin	Humanized, IgG1κ, anti-HER2	Oncological	09/25/98 (US) 08/28/00 (EU)
Gemtuzumab ozogamicin	Wyeth Madison, New Jersey	Mylotarg	Humanized, IgG4κ, anti-CD33; immunotoxin	Oncological	05/17/00 (US)
Alemtuzumab	Genzyme Cambridge, Massachusetts	Campath-1H	Humanized, IgG1κ, anti-CD52	Oncological	05/07/01 (US) 07/06/01 (EU)
Ibritumomab tiuxetan	Biogen Idec	Zevalin	Murine, IgG1κ, anti-CD20; radiolabeled (Yttrium 90)	Oncological	02/19/02 (US) 01/16/04 (EU)
Adalimumab	Abbott Deerfield Park, Illinois	Humira	Human, IgG1κ, anti-TNFα	Immunological	12/31/02 (US) 09/1/03 (EU)
Omalizumab	Genentech	Xolair	Humanized, IgG1κ, anti-IgE	Immunological	06/20/03 (US)
Tositumomab-I131	Corixa Seattle	Bexxar	Murine, IgG2aλ, anti-CD20; radiolabeled (Iodine 131)	Oncological	06/27/03 (US)
Efalizumab	Genentech	Raptiva	Humanized, IgG1κ, anti-CD11a	Immunological	10/27/03 (US) 09/20/04 (EU)
Cetuximab	Imclone Systems New York	Erbitux	Chimeric, IgG1κ, anti-Epidermal growth factor receptor	Oncological	02/12/04 (US) 06/29/04 (EU)
Bevacizumab	Genentech	Avastin	Humanized, IgG1, anti-vascular endothelial growth factor	Oncological	02/26/04 (US) 01/12/05 (EU)
Natalizumab[1]	Biogen Idec	Tysabri	Humanized, IgG4κ, anti-α4-integrin	Immunological	11/23/04 (US)

See Box 1 for methodology.

[1]Voluntary suspension of natalizumab marketing announced February 28, 2005.

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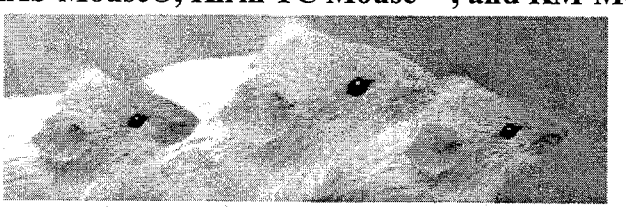
HuMAb-Mouse®, Kirin TC Mouse™, and KM-Mouse®:



- **HuMAb-Mouse:** Transgenic mice: the mouse genes for creating antibodies have been inactivated and replaced by human un-rearranged antibody genes.
- **Kirin TC Mouse:** complete sets of the variable and constant genes in human immunoglobulin loci. These transchromosomic mice can generate all of the human antibody genes, including all heavy chain classes that encode all isotypes (IgG1-4, IgA1-2, IgD, IgM and IgE).
- **KM-Mouse:** crossbred mouse of HuMAb-Mouse and Kirin's TC Mouse to produce all human antibody isotypes with an immune response we believe previously unseen in any human antibody producing mouse system.

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Medarex Locations

▪ Milpitas and Sunnyvale CA - Research and Development	~170
▪ Princeton, NJ - Headquarters ▪ Bloomsbury, NJ - Development (upstream and downstream) - QC - Clinical Operation ▪ Annandale, NJ - GMP manufacturing - QA	~290
Subtotal:	~460

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Medarex, Inc.

James D. Watson Helix Award for Mid-Cap Biotechnology Industry Leadership (2004)

24 UltiMAb products in clinical trials

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Broad Clinical Pipeline – Medarex and Partners

Phase I	Phase I/II	Phase II	Phase III
MDX-1307 Cancer **CNTO 95 – Centocor** Cancer **NVS Ab #1 – Novartis** Autoimmune Disease **NVS Ab #2 – Novartis** Autoimmune Disease **AMGN Ab #2 – Amgen** Undisclosed **AMGN Ab #3 – Amgen** Undisclosed **FG-3019 – Fibrogen** Idiopathic Pulmonary Fibrosis **NGS-TR2J – Kirin** Cancer **LLY Ab – Eli Lilly** Undisclosed **MDX-066 – MBL** C.Difficile Toxin A Disease **MDX-1100** Ulcerative Colitis **MDX-1303 –PharmAthene** Anthrax	**MDX-018 – Genmab** Undisclosed **MDX-214** EGFR+ Cancers **HuMax-EGFR – Genmab** Head and Neck Cancer	**CNTO 1275 – Centocor** Inflammation **AMG 714 – Genmab** Rheumatoid Arthritis (RA) **MDX-060** Hodgkin's Disease, ALCL **MDX-070** Prostate Cancer **AMGN Ab #1 – Amgen** Undisclosed **HuMax-CD20 – Genmab** RA, Lymphoma	**MDX-010 – BMS** Melanoma **HuMax-CD4 – Genmab** Lymphoma **CNTO 148* – Centocor** Inflammation

IND Prep	
MDX-1103 – MedImmune Lupus	**MDX-1106 – Ono** Cancer
MDX-1333 – MedImmune Lupus	**NI-0401 – NovImmune** Autoimmune Disease

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* Phase III trials expected in 2005/06

Medarex Partnerships

Abbott Laboratories
Amgen, Inc.
Amrad Corporation Limited
Athersys, Inc.
Avalon Pharmaceuticals, Inc.
BioWa, Inc.
Biosite Incorporated
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Cell Genesys, Inc.
Centocor, Inc. (Johnson & Johnson)
Corixa Corporation
Cyto Pulse Sciences, Inc.
Cytos Biotechnology AG
deCODE genetics, Inc.
diaDexus, Inc.
Diatos SA
Diversa Corporation
Eli Lilly & Company
Epigen, Inc.
Ferric Technologies, Inc.
FibroGen, Inc.
Gemini Genomics plc
Genesto A/S
Genmab A/S
Human Genome Sciences, Inc.
IDM Pharma, Inc.
Imclone, Inc.
Immusol, Inc.
Incyte Genomics, Inc.
Kirin Brewery Co., Ltd.
Kyto Biopharma, Inc.
Massachusetts Biologic Laboratories
MedImmune, Inc.
MGI PHARMA, INC.
m-phasys GmbH
Neuro Therapeutics, Inc.
Northwest Biotherapeutics, Inc.
Novartis Pharma AG
NovImmune S.A.
Novo Nordisk A/S
Oncomab, Ltd., (PRIMABioMed)
Ono Pharmaceutical Co., Ltd.
Peregrine Pharmaceuticals, Inc.
PharmAthene, Inc.
Pfizer, Inc.
Protein Design Labs, Inc.
Raven Biotechnologies, Inc.
Regeneron Pharmaceuticals, Inc.
Sangamo BioSciences, Inc.
Schering AG
Schering Plough Corporation
Seattle Genetics, Inc.
Trillium Therapeutics Inc.
Xerion Pharmaceuticals AG
ZymoGenetics, Inc.

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Average Annual Returns 1926 - 2001

Investment	Average return
Large stocks	**12.7%**
Small stocks	**17.3%**
Long-term corporate bonds	**6.1%**
Long-term government bonds	**5.7%**
US Treasury bills	**3.9%**
Inflation	**3.1%**

Source: Stocks, Bonds, Bills, and Inflation Yearbook 2002, Ibboston Associates, Inc. Chicago.

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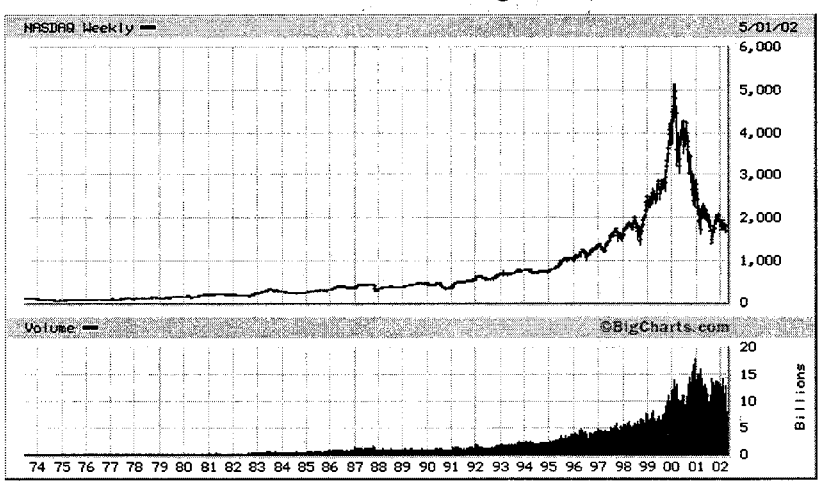
NASDAQ



Source: Stocks, Bonds, Bills, and Inflation Yearbook 2002, Ibboston Associates, Inc. Chicago.

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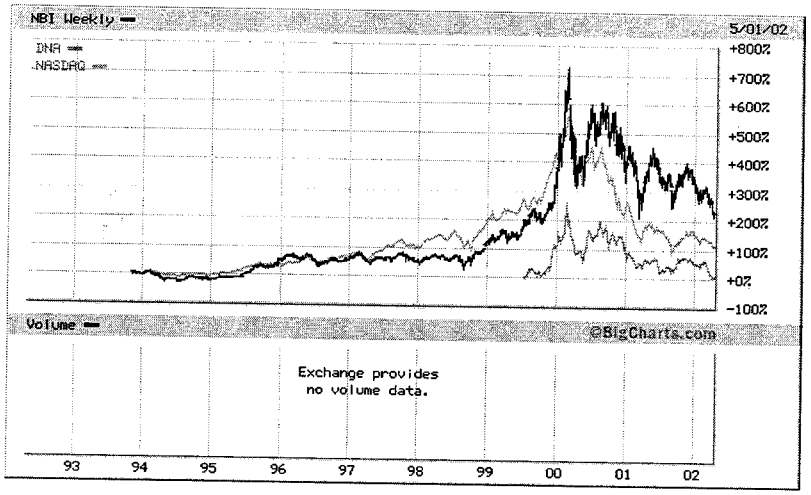
NASDAQ Biotech Index



Source: Stocks, Bonds, Bills, and Inflation Yearbook 2002, Ibboston Associates, Inc. Chicago.

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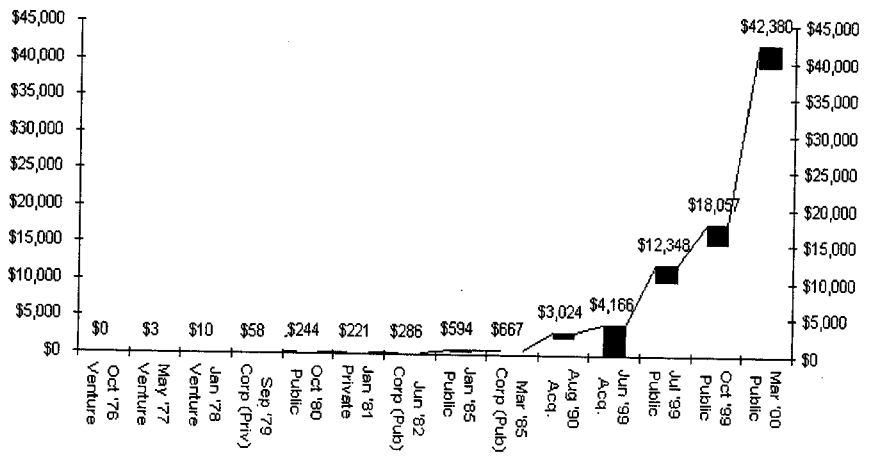
Genentech



Source: Historical Stock Price Data on Genentech, Price-Data.com

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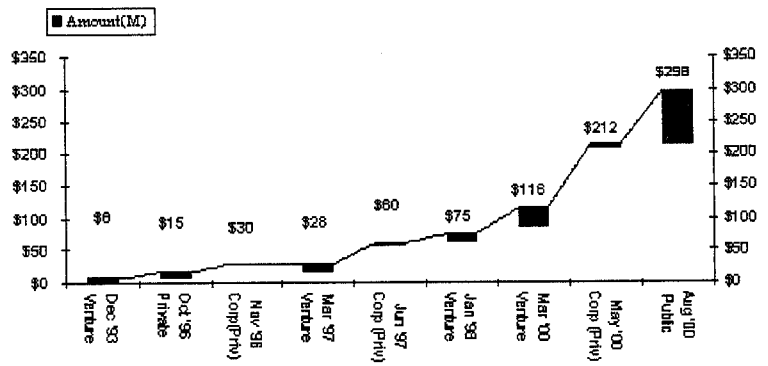
3-Dimensional Pharmaceuticals



Source: Historical Stock Price Data on 3-Dimentional Pharmaceuticals, Price-Data.com

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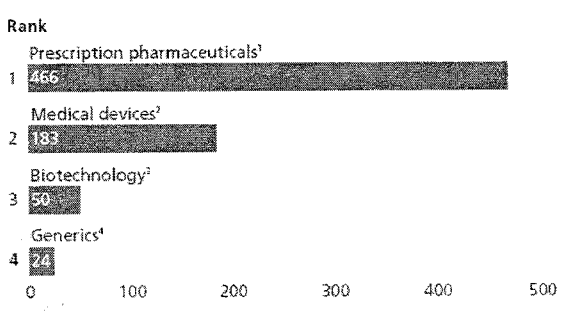
Global revenue for the major sub-sectors of the life sciences industries



Sources: Advanced Medical Technology Association, IMS Health, Generic Pharmaceutical Association.

[1]2003 constant US$ in 13 major markets, includes sales of generics.
[2]2002.
[3]Estimate obtained from pooling sales of leading biotech firms.
[4]2003, Europe and US markets only.

Source: The Future of the Life Sciences Industries, A Deloitte white paper developed in collaboration with the Economist Intelligence Unit. 2005

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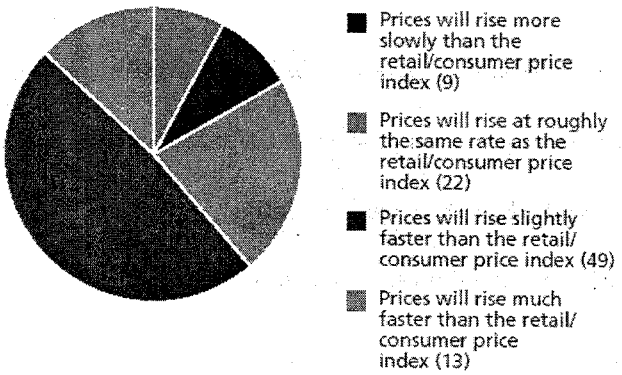
Between now and 2015, how do you expect the prices of drugs and medical devices to change?

% respondents



Source: The Future of the Life Sciences Industries, A Deloitte white paper developed in collaboration with the Economist Intelligence Unit, 2005

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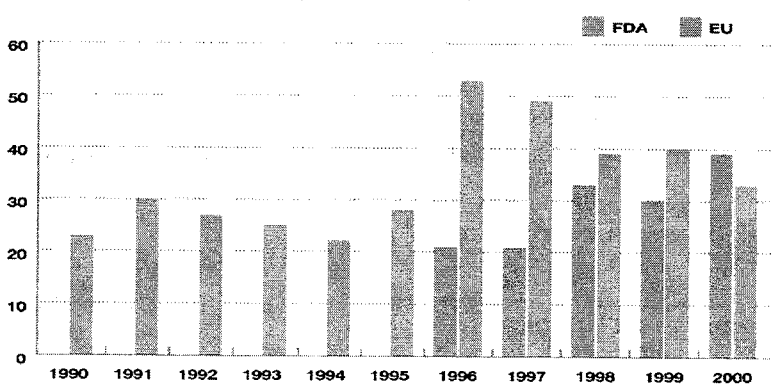
US Food and Drug Administration (FDA) and EU (European Union) approvals of new drugs per year.

Source: A. Moore, The big and Small of Drug Discovery, *EMBO Report*, Vol. 4 (2), p114-117, 2003



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Risk

- **Market Adoption Risk:** Demand for a new product is usually unknown in advance.
- **Technology Risk:** it is unknown whether a new technology will work.
- **People Risk:** experienced people to manage the company and finance.
- **Regulatory Risk:** Government regulation.
- **Exit Risk:** IPO, acquisition, buyout, or write off.

Source: R. Wustenhagen & T. Teppo, What makes a good Industry for Venture Capitalists? IWO Discussion Paper # 114, 2004

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Three Factors to be Success in Biotechnology Industry

1. **A quality management team**
   Scientific and business person in early stage.
   Market and sale in late stage.

2. **Adequate finance (Capital)**
   ~$ 300M to develop a product, IPO and several rounds of financing.

3. **Access to new technology**

Source: H.J.P. Schoemaker and A.F. Schoemaker, The three pillars of Bio-entrepreneurship, *Nat Biotechnol.* 1998;16 Suppl:BE13-15.

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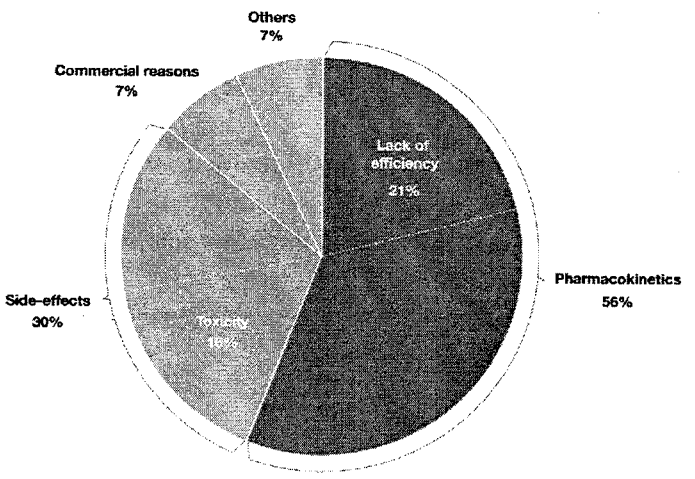
Major stumbling blocks for new drugs (industry averages during 1996–2000)

Source: A. Moore, The big and Small of Drug Discovery, *EMBO Report*, Vol. 4 (2), p114-117, 2003



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4 P to success

- **Passion to pursue the dream**
- **Persistence, learning from the mistakes and move on.**
- **Personality, practice, refine, personal and social awareness and management skills.**
- **Profile for risk, willing to rid to the right side.**

Source: Steve Onody, former CEO of Colorado MedTech, independent medical device consultant.

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Model for Success

- **Understand the basic technology that you propose to adapt.**
- **Align with a partner to enhance core potential.**
- **Take regulatory framework into consideration.**
- **Enter into proper legal documentation before commencing the work.**
- **Be prepared to adapt changed strategy while during the development process.**

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Biotech Profile in US

- **~2,000 biotech companies, ~130,000 employee**
- **~300 public and ~1,700 private**
- **~$ 65B invested and market value ~$ 110B**
- **Proteins and antibodies (big molecules) ~$ 33B sales in 2003 and estimated ~$ 60B in 2010.**
- **18 FDA approved therpeutical antibodies in market, 147 antibodies in clinical trials.**

- L. Jarvis, Will mabs mania CMOs?, Chemical Market Reporter, New York, Vol. 267 (15), p17-19, 2005
- H.J.P. Schoemaker and A.F. Schoemaker, The three pillars of Bio-entrepreneurship, *Nat Biotechnol.* 1998;16 Suppl:BE13-15.

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Asian Bio-Industry

Singapore, Taiwan, Korea and Australia are leading the way, but China could soon be a power as well, once intellectual property (IP) rights enforcement is addressed by its accession to the World Trade Organization (WTO). India has similar domestic IP concerns.

Source: CM Tang, MA Mahmud, FK Foo, SYe Chu , IT Chiu, M Tanticharoen, L Zhang & TW Chang, Realizing potential: the state of Asian bioentrepreneurship, *Nat Biotechnol.* 2003 Jul;21 Suppl:BE15-22.

Estimated number of biotechnology-related ventures in selected Asia-Pacific countries (2003)

Country	Estimated number of biotechnology ventures
China (Hong Kong)	100 (50)
Japan	140
Korea	300
India	170
Australia	200
Taiwan	100
Singapore	30
Malaysia	4

Source: CM Tang, MA Mahmud, FK Foo, SYe Chu , IT Chiu, M Tanticharoen, L Zhang & TW Chang, Realizing potential: the state of Asian bioentrepreneurship, *Nat Biotechnol.* 2003 Jul;21 Suppl:BE15-22.

Resources in Korea Biotechnology

- **Five-Year Plan for Science & Technology Innovation, enacted in 1997.**
- **Biotechnology 2000 (established in 1994) aims to bring Korean biotechnology to the same level as the world's leading industrialized countries by 2010. Total commitments are around US$15 billion.**
- **The 21st Frontier R&D program (started in 1999). It will support a total of 20 projects from functional genomics to plant biodiversity. Total R&D spending rising from 3.6% (US$3 billion) of the overall budget in 1998 to 4.7% (US$3.8 billion) in 2002.**
- **148 VC firms in Korea today—more than double the number registered a year ago. Total amounts available for venture investments are in the region of US$8.5 billion.**
- **A number of *chaebols* (conglomerates), such as the LG Group, SK Group and Samsung, have also set up their own VC funds to either support their own pharmaceutical activities.**
- **A highly trained labor force and a high level of entrepreneurism (the highest number of entrepreneurs per unit of population in Asia and one of the highest in the world.)**

Source: CM Tang, MA Mahmud, FK Foo, SYe Chu , IT Chiu, M Tanticharoen, L Zhang & TW Chang, Realizing potential: the state of Asian bioentrepreneurship, *Nat Biotechnol.* 2003 Jul;21 Suppl:BE15-22.

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Navigation through the Land of Opportunity, Korea

- **Key scientific personnel with specific areas of expertise within the sector.**
- **Need sufficient commercialization success stories deriving from the country's own research efforts.**
- **Need government to implement a policy of separating the prescription and dispensing of drugs.**
- **Link between the Korean Food and Drug Administration and the Korean International Patent Office.**

Source: CM Tang, MA Mahmud, FK Foo, SYe Chu , IT Chiu, M Tanticharoen, L Zhang & TW Chang, Realizing potential: the state of Asian bioentrepreneurship, *Nat Biotechnol.* 2003 Jul;21 Suppl:BE15-22.

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New Wave – Monoclonal Antibody Therapeutics 2004

- 18 Mabs approved in US Market
- Biogen Idec's Rituxan and Johnson and Johnson's Remicade > $2B
- Abbott's Humira – $852M
- Imclone and BMS – $1B (forecast)
- Genentechs Avastin – $5B (forecast)
- 147 monoclonal antibodies in clinical development

Source: L. Jarvis, Will Mabs be CMOs?, Chemical Market Reporter, New York, Vol. 267 (15), p17-19, 2005

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Potential Opportunities

- Generic Drug
- Prescription Drug
- Contract Manufacture (Lonza, Celltrion, Angel etc.)
- Biotechnology (Maria Biotech by Park Se-Pill, Seoul National University by Professor Hwang Woo-Suk)

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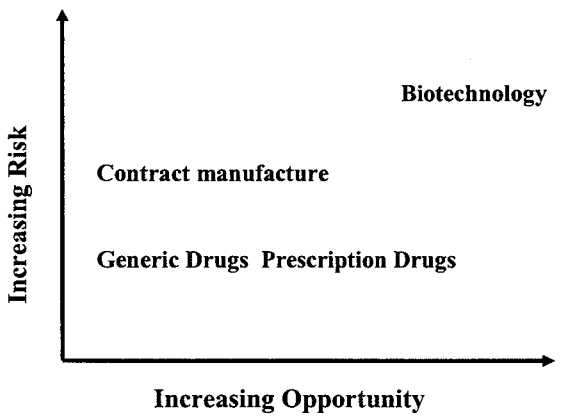
Risk and Opportunity Analysis



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Thank You.

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