

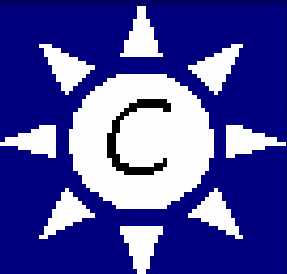
Biotech Pipeline & the Future Impact on Community Pharmacy

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Today's Objectives

- Biotechnology trends
- Market forecast
- Focus on the pipeline: what does it look like?
- Understand the nation's evolving prescription medicine supply systems: market responsive and efficient
- What does it mean for pharmacy?
- Name things you can do to position yourself to play these new roles.

Biotechnology is One of the Major Forces Changing Health Care

- **Biotechnology explosion**
- **Telemedicine/Internet explosion**
- **Rising use of alternative therapy**
- **Rising consumer activism**
- Treatment will move:
 - from disease to prevention
 - from institutions to home
- Will blur lines between distribution/delivery-- redefining getting product to the right place at the right time to the right provider to the right patient



The Human Genome & Biotechnology

- “A milestone in biology unlike any other.”
- “We’ve called the human genome the book of life, but it’s really 3 books: It’s a history book. It’s a shop manual and parts list. And, it’s a textbook of medicine more profoundly detailed than ever.”

*---Francis Collins, director NHRI
director*



- The HGP could fundamentally restructure the nation’s \$1.3 trillion healthcare industry in the next 20-30 years: PwC/Russ Coile
- June 26, 2000; 5-years ahead of schedule
- A short 50 years after the discovery of DNA by Watson and Crick in 1953

Development is evolutionary...

1970: First enzyme discovered to cut DNA molecules at a specific site

1971: First complete synthesis of a gene

1972: First time DNA fragments linked

1976: First NIH research guidelines

1980: Oil-eating microbes patented by Exxon

1982: First recombinant DNA vaccine for livestock

1983: First whole plant grown from biotechnology

Development is evolutionary...

1986: First genetically engineered vaccine for humans: Hep B

First anticancer drug through biotech: interferon

1990: First food product from biotech approved: modified yeast

1994: First FDA approval for food product

1997: First weed & insect resistant crops developed

First cloned animal: Hello Dolly!



Development is evolutionary...

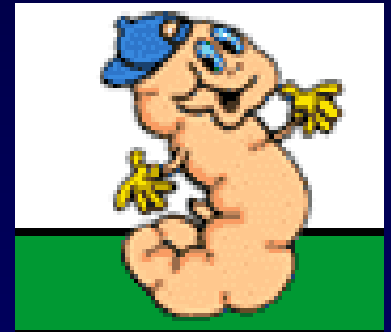
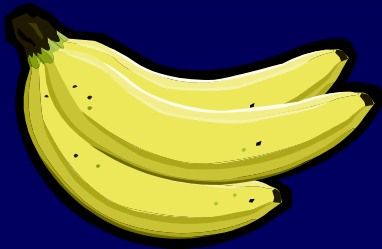
2000: First complete plant genome mapped
108.9 million acres of biotech crops grown in
13 countries

2004: First genetically modified pet: the
GloFish

2004: About 25% of all prescription products
on market since 2000 are from
biotechnology

The Human Genome: Fun Facts

- 30,000-40,000 genes not the 100-120,000 thought earlier
- Five times as many as in baker's yeast
- About twice as many as that needed to grow a worm or fly!
- Bananas share about $\frac{1}{2}$ our genome while mice share 90%!

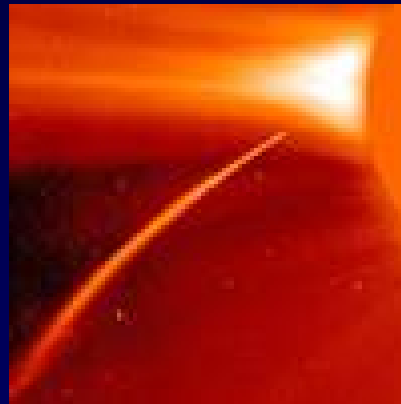
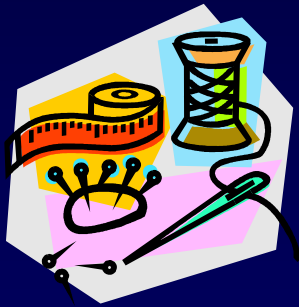
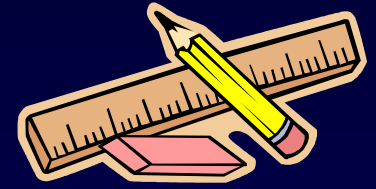


- BUT, each single human gene can make 10 proteins vs. a worm or fly's genes making just one or two.
- "We have the Cuisinart vs. the paring knife

--Francis Collins

The Human Genome: Fun Facts

- "Life's Blueprint in Less than an Inch"-the Washington Post
- 5 million strands of DNA can fit through the eye of a needle



- All our DNA laid end to end would go to the sun and back 400 times!
- The genetic instructions for making a person take up less than 1" of the 6-ft long strand of DNA in each cell
- Yet, DNA is a vibrant ecosystem of its own

Biotechnology Definition

- **OLD:** Recombinant genetic engineering...using biological processes to develop products
- **NEW:** Life sciences...biology/chemistry technology affecting discovery and development of products for:
 - Human healthcare (therapeutics, diagnostics, drug delivery, cell and gene therapy...even moving toward some devices and drug/device combinations)
 - Wellness...not just sickness
 - Agriculture (food, feed, fibers, transgenics)
 - Environment (bio-remediation)
 - Bio-based industrial processes and efficiency
 - Bio-based energy–Supply (reagents, biologicals)
- All driven by a new set of enabling technology (genomics, combinatorial chemistry, SNPs, proteomics, etc.)

Source: Burrill and Company

Biotechnology Contributions

- Industrial biotech: ethanol energy alternatives:
1 gall = 30 imported oil
- Reduce water consumption by 30-50% in textile production
- Bioplastics: reduce plastics in waste stream by 80%
- See
www.bio.org/ind/pubs/cleaner2004/CleanerReport.pdf

Biotechnology Contributions

- Agriculture biotech: 11,000 field trials on 81 different transgenic crops since 1987
- UN's Food & Ag Org confirms safety
- Address global food needs
- 67.7 million hectares in 2003
- Corn, soybeans, cotton and canola
- Consumers still wary



Biotechnology Will Transform Industries, Including Health Care

- Industrial convergence of farmers, doctors, drugmakers, chemical processors, computer and communication companies, energy companies and many others into the business of life science.
- Will revolutionize healthcare and transform economics of the Rx business. Will need to craft ways of dealing with industry's new economic landscape.



A single herd of goats may soon replace a \$150 million drug factory...HBR 4/2000

Promises and Implications BIG*

Promise:

- Rapid technological innovation and vast number of new targets identified: epilepsy, deafness, color blindness, muscular dystrophy-- by 2010, a dozen predictive tests
- Today 150 targets, tomorrow 5-10,000
- Rapid acceleration in pace of new therapeutic introductions
- Drugs and treatments that are more tailored to specific patients

Implications:

- *Development* becomes a bottleneck
- Shorter product life cycles
- Market fragmentation
- Blurring distinction between "product"
and "service"

* Gary Pisano, HBS 3/2000

Future Environment

Customization of medicine



Present	Future
Disease by symptoms–diagnosis	Disease by mechanics–prognosis
Disease uniformity–guidelines, formularies	Disease heterogeneity–customization, targeted Rx
Patient uniformity–care standards	Patient variability–tailored care
Blockbusters–Universal Rx	Multibusters–pharmacogenetics
Consumer ignorance–acute care	Consumer empowerment–preventive care

Personalized Medicine

- Genetic testing becomes routine
- Diseases will be understood at a molecular level
 - –Proteins, pathways, mechanisms
- Patient populations at risk for ADR will be identified
- Targeted clinical trials patient selection
- Healthcare moves to predictive, preventative care with pre-symptomatic Dx and Rx routine
- FDA Guidance on Pharmacogenomics: 11-2003

Market Forecast

- \$47 billion global biotech revenue 2003
 - USA: 77%
 - Europe: 16%
 - Canada: 3.7%
 - Asia-Pacific: 3.3%
-
- USA Today, June 8, 2004

US, European, Canadian & Australian Biotech

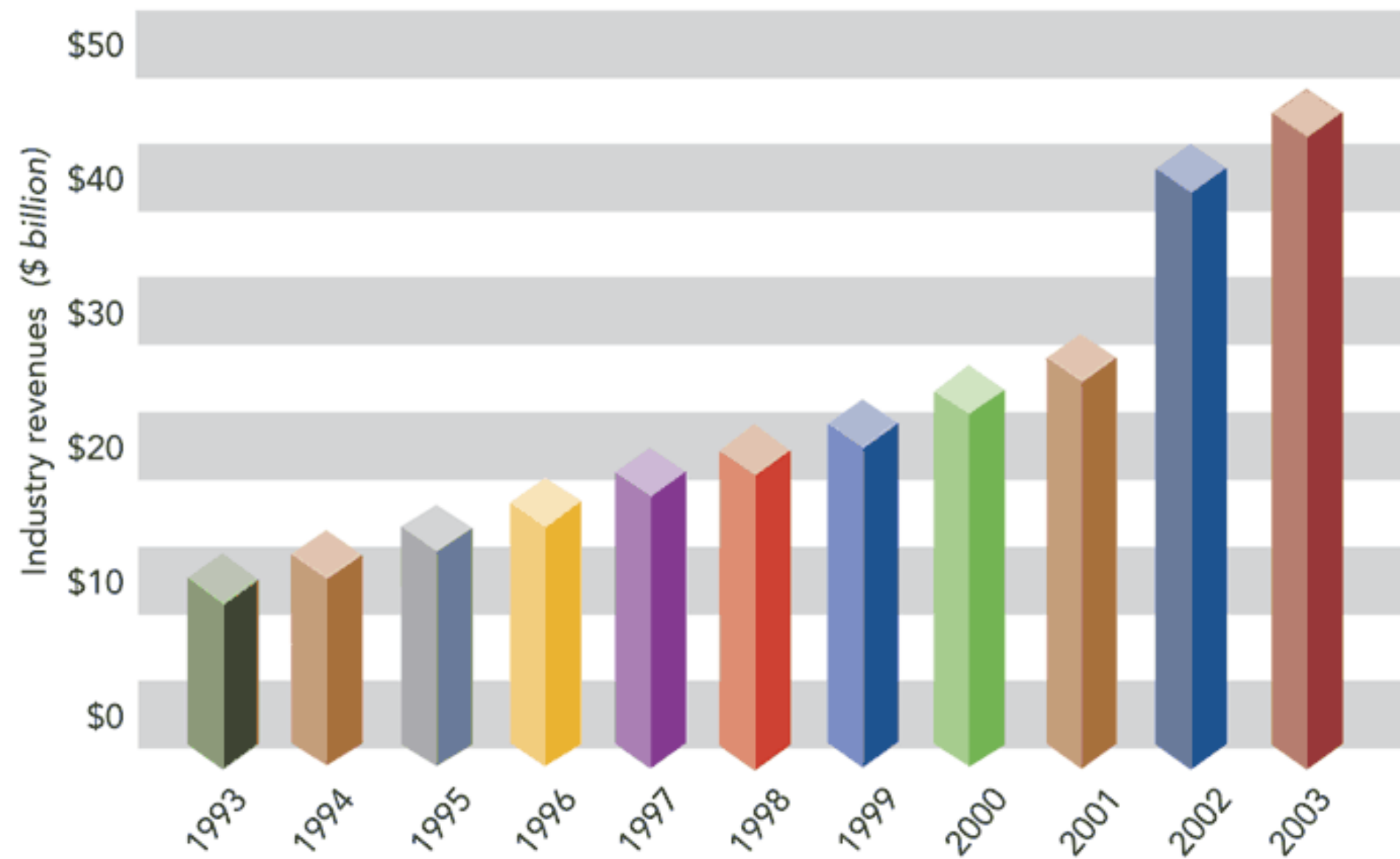
All numbers reported year-end 2003 unless otherwise noted

	USA	Europe	Canada	Australia
Sales/ Revenue	\$45.2 B	\$8.3 B	\$1.5 B	\$0.9 B
Annual R&D	\$13.3 B	\$5.0 B	\$0.6 B	\$0.1 B
Number of Companies	1,455	1,878	417	214
Number of Employees	143,000	33,300	7,800	6,500
Number of Public Cos.	315	102	85	50
Market Capitalization	\$342 B	\$25 B	\$8.8 B	\$4.1 B

Source: Burrill & Company, Ernst & Young

[Figure 3.1]

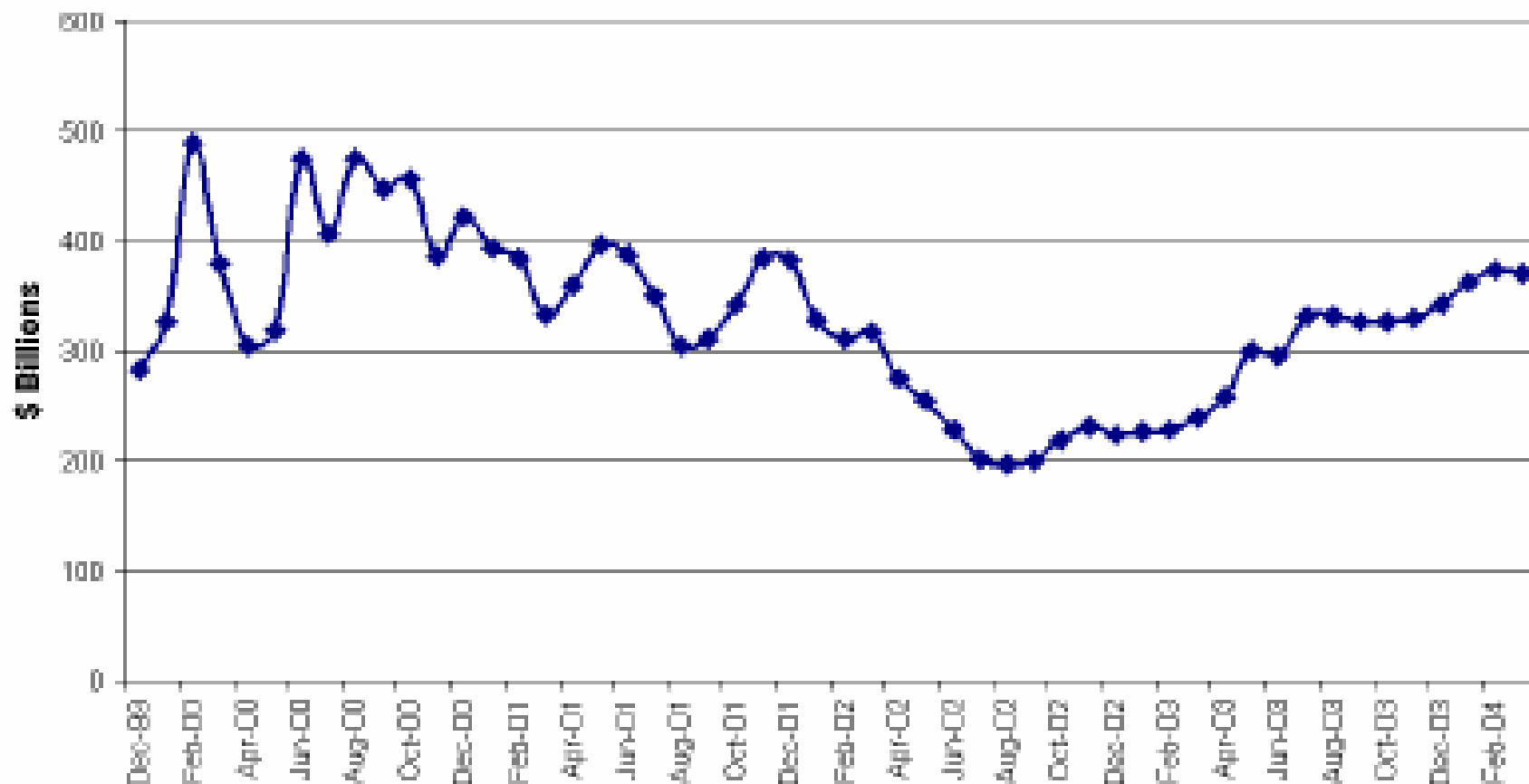
US BIOTECHNOLOGY INDUSTRY REVENUES INCREASE



Source: Burrill & Company

Historical Biotech Market Cap

Biotech Industry Market Cap by Month



Biotech Market Trends 2003

- Re-emerged after 3-year devaluation
- Burrill Biotech Select Index rose 66%
- Industry's market cap up 53%
- Raised more than \$16 billion—second best year on record
- 7 companies went public in 2003, raising \$453 million

Biotech and Pharma: Comparison

- Pfizer/Merck
 - Combined 35+ (with merger of Pharmacia) products on the market (prescription drugs)
 - Combined 70+ products in the clinic and expect to send 26 new medicines and vaccines to the FDA for approval over the next 4 to 5 years
 - Combined 2003 (12 months trailing) revenue: \$85 billion
 - Biotech Industry
 - 155 drugs on the market
 - >370 drugs in the clinic or awaiting FDA approval
 - Aggregate 2003 revenue: \$45 billion
- Source: Burrill and Company

Biotech Forecast 2004

- Still changed market dynamic post ImClone: invest later after risk reduced
- Overall, industry still undervalued
- Value gains of 25-40%
- Estimate \$20 billion raised in markets
- 25-30 IPOs in 2004
- Supply of deals will be more than demand
- More PhRMA consolidation and biotech deals
- More linkage between Rx and Dx:
Theranostics

[Figure 3.5]

PERFORMANCE OF TOP TEN BIOTECH COMPANIES BY REVENUE
FIRST QUARTER 2004

COMPANY	Q1 03 REVENUE (\$ million)	Q1 04 REVENUE (\$ million)	PERCENT CHANGE IN REVENUE	2003 Q1 MCAP (\$ million)	2004 Q1 MCAP (\$ million)	PERCENT CHANGE IN MCAP
Amgen Inc.	\$2,343	\$1,761	33%	\$74,292	\$74,136	0%
Genentech Inc.	\$787	\$596	32%	\$56,275	\$17,855	68%
Serono SA	\$557	\$442	26%	\$13,779	\$10,726	22%
Biogen-IDEC Inc.	\$542	\$437	24%	\$18,891	\$5,308	72%
Genzyme Corporation	\$491	\$314	56%	\$10,597	\$7,866	26%
MedImmune Inc.	\$489	\$435	12%	\$5,731	\$8,267	(44%)
CHIRON Corp.	\$380	\$307	24%	\$8,252	\$6,990	15%
Gilead	\$309	\$165	87%	\$11,861	\$8,377	29%
Cephalon Inc.	\$215	\$145	48%	\$3,199	\$2,205	31%
Elan PLC	\$159	\$225	(29%)	\$8,015	\$978	88%

* 12-months trailing September 30

Source: Burrill & Company

Biotech Product Trends

- Development of biotech compounds is explosive
- More than 20% of new medicines globally and 4 of 5 in pipeline are from biotechnology
- Commercialization is beginning to blossom with rapid growth expected in the near term
- Most compounds focused in the oncology arena, followed by infectious disease, CV and neuro
- Most compounds in development will be additive or complimentary to current therapies
- Breakthrough treatments may provide new hope of some diseases
- Biogenerics issue

[Figure 3.12]

BIOTECH DRUGS EXPOSED TO NEAR TERM PATENT EXPIRATION

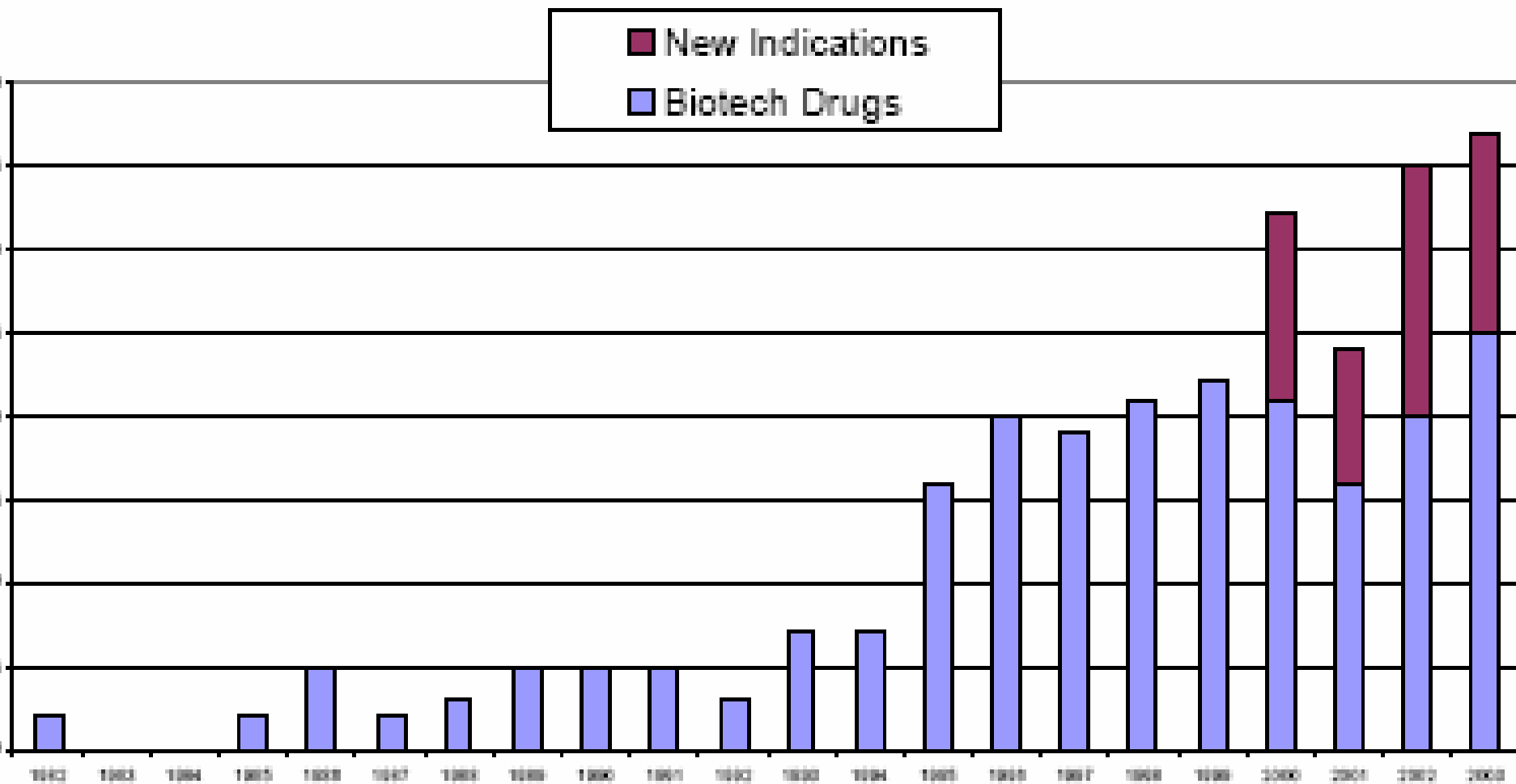
BRAND (CHEMICAL)	US PATENT EXPIRATION	MARKETER	INDICATION
Avonex (interferon alfa-2b)	2003	Biogen	Multiple sclerosis
Humatrope (somatropin)	2003	Eli Lilly	Growth hormone deficiency
Nutropin/Nutropin AQ (somatropin)	2003	Genentech	Growth hormone deficiency
Epogen (epoetin alfa)	2004	Amgen	Anemia
Geref (sermorelin)	2004	Serono	Growth hormone deficiency
Procrit (epoetin alfa)	2004	Ortho Biotech	Anemia
Synagis (palivizumab)	2004	Abbott	Respiratory syncytial virus
Activase (alteplase)	2005	Genentech	Myocardial infarction, stroke, pulmonary embolism
Protropin (somatrem)	2005	Genentech	Growth hormone deficiency
Neupogen (filgrastim)	2006	Amgen	Neutropenia

Source: ABN Amro and Burrill & Company

Biotech Rx Product Pipeline

- 155 drugs on the market
- >370 drugs in the clinic or awaiting FDA approval
- Aggregate 2003 revenue: \$45 billion
- 25 new products in 2003, up 25% from 2002
- 5-Cancer, 1-HIV, 3-orphan, intranasal Flu

Number of Products Approved 1980–2003



[Figure 3.4]

A NUMBER OF FIRSTS

- Aldurazyme is the first drug approved for Mucopolysaccharidosis-1
- Amevive is the first biologic approved for psoriasis
- Fabrazyme is the first drug approved for Fabry's disease
- Fuzeon is the first fusion inhibitor approved for HIV/AIDS
- Namenda is the first drug for mild to moderate Alzheimer's
- Velcade is the first-in-class proteasome inhibitor for relapsed and refractory multiple myeloma
- Xolair is the first biologic approved for asthma

Source: BIO

Therapeutic Technologies

- Major research emphasis:
 - Vaccines (HIV, cancers)
 - Monoclonal antibodies
 - Antisense compounds (infectious diseases, CVD, inflammatory conditions)
 - Endothelin receptor antagonists (CVD)
 - Gene therapy (HIV, cancers)
 - Tumor necrosis factor targets (arthritis)

Therapeutic Technologies

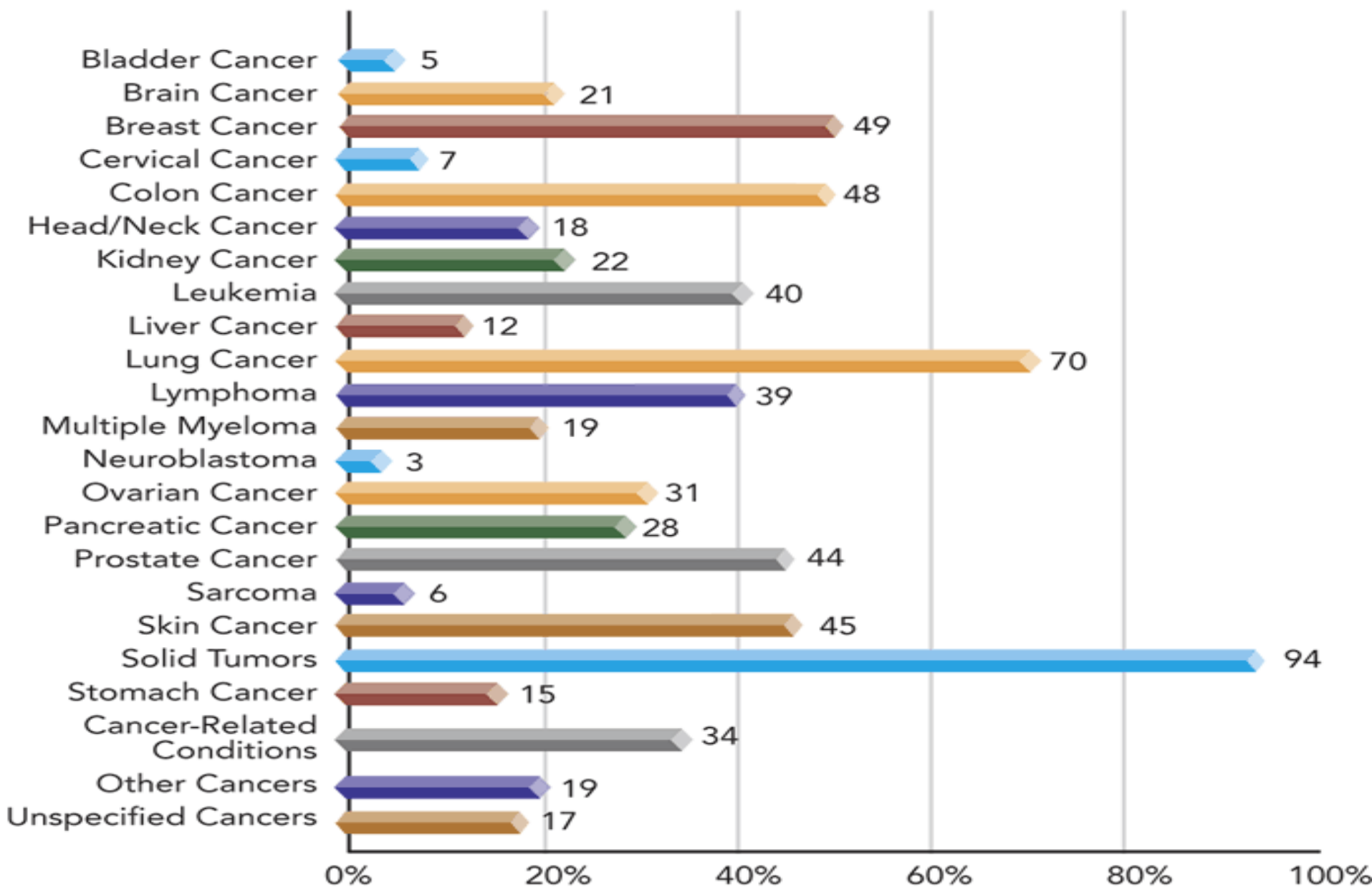
- Vaccines in development
 - HIV
 - Non-Small Cell Lung cancer
 - Breast cancer
 - Colon/colorectal cancer
 - Prostate cancer
 - Lymphoma

Pipeline Products: Cancer

- 556,500 will die in US 2003
- 10 million new cases reported in 2000
- Expected to rise to 15 million in 2020
- NCI goal: “elimination of suffering death from cancer by 2015”

[Figure 3.21]

MEDICINES IN DEVELOPMENT FOR CANCER*



* Some medicines may be listed in more than one category.

[Figure 3.20]

BIOTECH CANCER DRUGS AWAITING APPROVAL

DRUG	SPONSOR	DESCRIPTION	LAST REGULATORY ACTIVITY
Avastin	Genentech	An investigational therapeutic antibody designed to inhibit Vascular Endothelial Growth Factor (VEGF), a protein that plays a critical role in tumor angiogenesis and maintenance of existing tumor blood vessels. Avastin interferes with the blood supply to tumors, a process that is critical to tumor growth and metastasis.	Received Fast Track Status from FDA in Jun
Combretastatin	Oxigene	One of a new class of therapeutic compounds known as vascular targeting agents, Combretastatin works by affecting the microtubules that form the cytoskeleton of the endothelial cells lining the tumor vasculature. Disrupting the structure makes the cells change shape which stops blood flow and starve the tumor of nutrients.	Received Fast Track Status from FDA in Jun
Erbix	ImClone	A highly specific monoclonal antibody that binds to EGFR and blocks the ability of EGF to initiate receptor activation and signaling to the tumor. This blockade results in an inhibition of tumor growth by interfering with the effects of EGFR activation including tumor invasion and metastases, cell repair and angiogenesis.	Resubmitted for FDA approval in Aug

Revimid	Celgene	A novel, small-molecule, orally available analog of thalidomide that is designed to be more potent and potentially have a superior safety profile than the parent compound. Revimid is being tested for treatment of relapsed or treatment-resistant multiple myeloma, a blood cancer.	Received Fast Track Status from FDA in Feb
Tarceva	Genentech and OSI Pharmaceuticals	One of a new class of cancer drugs known as epidermal growth factor inhibitors, which are designed to block a protein involved in cancer cell division. Tarceva would be given exclusivity if it is approved in the US to treat the most common form of brain cancer, malignant glioma	Received orphan status from FDA in Aug
Xyotax	Cell Therapeutics	A pharmaceutical that links paclitaxel, the active ingredient in Taxol, to a biodegradable polyglutamate polymer which results in a new chemical entity, designed to selectively deliver high and potentially more effective levels of active chemotherapeutics to tumors.	Received Fast Track Status from FDA in Jun

Source: Burrill & Company

Product Pipeline: Inf. Disease

- AIDS: 29 million of 42 million living with disease are in Africa
- Of the 42 million, 6 million need antiretrovirals but only 400,000 receive them
- BioVentures for Global Health
- SARS: development in full swing
- Antibiotic resistant bugs—"ribosomally synthesized antimicrobials peptides"--RAMPs

RAMPS UNDER DEVELOPMENT

COMPOUND	COMPANY	INDICATION	STATUS
Pexiganan (derived from a peptide in African clawed frog skin)	Genaera	infected foot ulcers in diabetes	Phase III
MBI-594 (indoliciden analog similar to those derived from bovine neutrophils)	Micrologix	acne infections	Phase II
P-113 (a peptide from human saliva)	Demegen	oral candidiasis	Phase I/II
rBPI-21 (peptide found in human neutrophils)	Xoma	pediatric meningococcermia	Phase III
rBPI-21	Xoma	Crohn's disease	Phase II
Iseganan (a peptide in pig leukocytes)	Intrabiotics	ventilator pneumonia	Phase II/III

Source: *The Scientist*

Vaccine Development Continues

- 100 vaccines in development
- \$750 million RD annually
- From West Nile, Herpes to traditional diseases
- 50 for cancers
- Biothreats-anthrax, etc.

[Figure 3.24]

POTENTIAL VACCINE TREATMENTS IN THE PRODUCT PIPELINE

COMPANY	VACCINE UNDER DEVELOPMENT
Merck	Cervical cancer-causing human papilloma viruses
GlaxoSmithKline	Herpes
Acambis	West Nile Virus
VaxGen	AIDS: gp 120 surface protein; Phase II trials in US and Thailand
VaxGen/ Aventis Pasteur	AIDS: gp 120 +ALVAC (HIV genes in canary pox virus) Phase II trial to start in Thailand
Oxford University	AIDS: HIV genes in naked DNA; Phase I/II trials in UK
Nairobi University	AIDS: HIV genes in pox virus; Phase I trial in Kenya
Merck	AIDS: HIV genes in naked DNA; Phase I trials in US
Merck	AIDS: HIV genes in common cold virus; Phase I trials in US
Biovector Therapeutics	AIDS: Lipopeptides; Phase I trials in France
VaxGen/Chemo-Sero- Therapeutic Institute	Smallpox: LC 16-Kaketsuken

Dendreon
Cancer (prostate): A stage III trial showed the Provenge vaccine delayed the onset of disease-related pain in patients with a certain level of hormone-resistant prostate cancer

Merck
Shingles

Merck
Diarrhea in babies: mitigate the rotovirus that causes it

National Cancer Institute
Cancer: Tricom, a vaccine that is increasing the life span of cancer patients

IDEC Pharmaceuticals/
Genentech
Cancer: non-Hodgkin's lymphoma, Rituxan rituximab anti-CD-20 antibody

Dendreon
Cancer: Provenge; Stage III trials, T-cell proliferation ELISPOT assay that co-cultures a patient's T-cells and antigen presenting cells to determine T-cell response to therapies

Antigenics Inc.
Cancer: Oncophage, a dendritic cell vaccine that determines T-cell Response to therapies

Source: BioCentury

[Figure 3.26]

SELECTED COMPANIES INVOLVED IN DEVELOPING VACCINES AS COUNTERMEASURES

COMPANIES	VACCINES
Acambis	Live vaccines (Smallpox)
Avant Immunotherapeutics	Attenuated bacterial vaccines (anthrax)
Coley Pharmaceuticals	Vaccines using proprietary CpG oligos to stimulate immune-response recombinant subunit vaccines (anthrax)
Dor BioPharma	Microencapsulation delivery for recombinant subunit vaccines (anthrax)
DynPort Vaccine	Prime contractor for the DoD's Joint Vaccine Acquisition Program
MacroGenics	Proteomics and antibody engineering vaccines (plague, smallpox, anthrax)
Microscience	Oral anthrax vaccine
Siga Technologies	Live recombinant vaccines (anthrax, smallpox)
Vical	Naked DNA vaccine (anthrax)

Source: Genetic Engineering News

Product Pipeline: Gene Therapies

- Back to the basics
- Ways to change, remove, add genes
- Viral vectors
- Single/Few gene defect diseases:
 - ALS, Parkinson's, Sickle Cell

[Figure 3.29]

SELECTED BIOTECHNOLOGY FIRMS CONDUCTING RESEARCH
IN GENE THERAPY INVOLVING THE BRAIN

FIRM	INDICATION	APPROACH	RESEARCH STAGE
Ceregene	Alzheimer's disease	Gene nerve growth factors delivered in cells via adeno-associated viral (AAV) vector to enhance survival of neurons involved in memory	Phase I
	Parkinson's disease	Glial cell line derived neurotrophic factor delivered via AAV vector to protect dopamine-producing neurons	Preclinical
	Amyotrophic lateral sclerosis	Growth factor genes to enhance function and slow degeneration of neurons	Preclinical
Neurologix	Parkinson's disease	Genes for glutamic acid decarboxylase (GAD) delivered via AAV vector to decrease symptoms	Phase I

Oxford BioMedica	Parkinson's disease	Gene delivery via Equine Infectious Anemia lentivirus to boost production of dopamine	Preclinical
NsGene	Parkinson's disease	Cell-based gene production of neurotrphic factor to protect and enhance nerve cell survival	Preclinical
	Alzheimer's disease	Cell-based gene production of nerve growth factor	Preclinical
Genzyme	Type A Niemann-Pick disease	Delivery of acid sphingomyelinase gene into the brain via AAV vector to boost enzyme production	Preclinical

Source: Nature Biotechnology

Product Pipeline: Alzheimer's

- Reagan's death prompts more discussion
- No. 1 cause of institutionalization affecting 4.5 million
- 60 companies working on therapies
- 40 in human trials
- 200 failed drugs since 1992

SELECTED BIOTECH RESEARCH FOCUSING ON IMPROVING THE LONG-TERM PROGNOSIS FOR ALZHEIMER'S PATIENTS

COMPANY

AIM

STATUS

STRATEGY

Immusol

Generate a 'phenotype of survival' in cells exposed to conditions that normally result in apoptosis (cell death)

Early stages

Cells which avoid death in selection system owe their survival to the 'switching-off' of a crucial gene involved in apoptosis. Create a population of cells target gene expression is blocked and expose them again to the selection leading to 'survival' phenotype.

Accera

Protect neurons by increasing rates of metabolism and glucose nutrition

Phase IIb trials, has FDA Fast Track status

Alzheimer's patients exhibit hypometabolism preceding the onset of dementia and is testing a product Ketasyn (AC1202) to provide an alternative source of energy for neuronal cells.

Pharmexa and Lundbeck

Vaccine to stimulate and immune response against undesirable proteins

Animal trials complete; Lundbeck will develop vaccine ME-106

AutoVac technology stimulates response against beta-amyloid without risking an autoimmune attack.

Ceregene

Increase nerve growth factor (NGF) for neural regeneration

Phase I completed, IND application filed

Use gene therapy to take dendritic cells from the skin and transform them with the NGF gene and inject them directly into the brain.

Samaritan

Protection against beta-amyloid toxicity in the brain

Testing in rats

Using cholesterol derivatives on neural stem cells.

Prana Biotechnology and University of Melbourne

Dissolve plaques caused by beta amyloid

Pilot clinical trial successful

Clioquinol (PBT-1) works by inhibiting zinc and copper ions from binding to beta-amyloid, helping to dissolve the protein and prevent it from accumulating.

D-Pharm

Bind metal ions selectively, rendering them safe, in a lipid membrane using a membrane activated chelator (MAC)

Entered Phase I trials

DP-109, an orally available MAC, binds metal ions and significantly reduces the uptake of beta-amyloid by neurons.

Targacept, Inc. and Medical College of Georgia

Insight into the pathways implicated in beta-amyloid-induced cell death

Three Phase II compounds one Phase I compound

Identified key enzyme SHP-1 that blocks the cellular pathway triggered by activation of the alpha-7 neuronal nicotinic receptor that protects against the negative effects of beta-amyloid.

Nymox

Underlying mechanisms of Alzheimer's disease

Holds global permit rights to the use of statin drugs in Alzheimer's

Targeting neural thread proteins, the marker measured in urine test for Alzheimer's Targeting spherons, tiny balls of protein in cells that enlarge as we age and then burst, creating senile plaques.

Neurochem Inc.

Prevent aggregation of beta-amyloid proteins around brain cells

Phase II trial completed

Alzhemed™ binds to soluble beta-amyloid to prevent formation of plaques and inhibits inflammatory response.

GB Therapeutics

Inhibit progression of disease

First human trial in January 2004 for GT 1061

Chemically altered properties of nitric oxide to create molecules called 'smart nitrates' that improve communication between neurons.

[Figure 3.30]

STATE OF THE ART FOR SMART:
COGNITIVE ENHANCEMENT DRUGS IN THE PIPELINE

TYPE OF DRUG	COMPANY	PURPOSE/TARGET	STATUS
CREB suppressor	Helicon Therapeutics	Suppression of disturbing memories	Early stages
CREB enhancer	Helicon Therapeutics	Memory enhancement-CREB is a protein that switches on the genes that control the release of neurotransmitters essential to long-term memory	Early stages-human trials
CREB enhancer MEM 1414	Memory Pharmaceuticals in partnership with Roche	Memory enhancement—inhibits an enzyme that breaks down cAMP, a key memory transmitter that activates CREB memory	Entering Phase I trials in early 2004
Calcium flow regulator MEM 1003	Memory Pharmaceuticals	Memory enhancement—restores the equilibrium of calcium MEM 1003 in brain cells that have been disrupted by Alzheimer's, mild cognitive impairment, or vascular dementia	Phase I trials

Phosphodiesterase (PDE) inhibitors PDE-4	Memory Pharmaceuticals and separately Helicon Therapeutics	Memory enhancement—allows more CREB to hang around the cell during learning promoting memory consolidation	Early stages
Ampakines CX516	Cortex Pharmaceuticals	Memory enhancement—amplifies the neurotransmitter glutamate, stimulating it to produce more synapses	Phase II trials
Gaba blocker SGS742	Saegis Pharmaceuticals	Blocks gaba, a neurotransmitter which can inhibit memory consolidation	Completed Phase II trials
Phenserine	Axonyx	Potent acetylcholinesterase inhibitor for the treatment of mild to moderate Alzheimer's	Completed Phase II trials

Source: *Scientific American and Burrill & Company*

[Figure 3.34]

SELECTED NEURAL GROWTH FACTORS UNDER DEVELOPMENT

NAME	FUNCTION	POTENTIAL DISEASE TARGETS	SOME COMPANIES INVOLVED IN RESEARCH
Brain derived neurotrophic factor (BDNF)	Keeps newborn neurons alive	Depression (abandoned for amyotrophic lateral sclerosis)	Amgen
Ciliary neurotrophic factor (CNTF)	Protects neurons from death	Huntington's disease (now testing against obesity)	Regeneron Pharmaceuticals
Epidermal growth factor (EGF)	Spurs stem cells in brain to divide	Brain tumors and stroke	ImClone Systems
Fibroblast growth factor (FGF)	In low doses, supports survival of various cell types; at high doses, induces cells to proliferate	Brain tumors and stroke	ViaCell
Glial cell lined-derived neurotrophic factor (GDNF)	Prompts motor neurons to sprout new branches, prevents cells that perish in Parkinson's disease from dying	Parkinson's disease and ALS	Amgen

Glial growth factor-2 (GGF-2)	Favors production of glial (support) cells	Spinal cord injury, multiple sclerosis and schizophrenia	Acorda Therapeutics
Insulinlike growth factor (IGF)	Fosters the birth of both neurons and glial cells	Multiple Sclerosis, spinal cord injury, ALS and age related dementia	Cephalon, West
Neurotrophin-3 (NT-3)	Promotes formation of oligodendrocytes (type of glial cell)	Multiple sclerosis, spinal cord injury and ALS	Amgen and Regeneron Pharmaceuticals

Source: *Scientific American*

Product Pipeline: Addiction

ADDICTION DRUGS IN THE PIPELINE

TARGET	COMPANY	PRODUCT	DESCRIPTION	STATUS
Alcoholism	Drug Abuse Sciences	Naltrexone Depot	Once a month injectable formulation of generic trial anti-addiction drug naltrexone. Naltrexone works by binding to the receptor to block the opiate euphoric effects of the drugs.	Phase III completed in 2nd Phase III trial. Filing for approval in 2004
Opiate Addiction		Naltrel		
Cocaine Addiction	DrugAbuse Sciences	DAS-431 IV	D1 dopamine receptor agonist that acts in the in prefrontal cortex.	Phase II trial
Nicotine Addiction	Addex Pharmaceuticals	ADX10061	Subtype selective D1 dopamine receptor antagonist.	Phase I trial
Nicotine Addiction	Xenova	TA-NIC	"Vaccine" that generates antibodies that will recognize nicotine by linking the small molecule to a large protein.	2nd Phase II trial
Cocaine Addiction	Xenova	TA-CD	"Vaccine" that works like TA-NIC.	Phase II trial
Opiate Addiction	WEX Technologies	Tetrodin	Using a derivative of tetrodotoxin (poison in Pufferfish) to reduce or eliminate withdrawal symptoms allow the body to clear the opiate residue.	Phase II trial

Source: Burrill & Company

Pipeline: Diabetes

- LAF237, Novartis, Phase II—a GLP1 peptide simulating insulin controlled blood sugar levels with few side effects
- Exenatide: Amylin and Lilly, long-lasting
- NN2211, Novo Nordisk, GLP1 mimic injection
- CJC-1131, ConjuChem, GLP1 mimic
- Albugon, HGS
- Inhalable insulin delivery system: BioSante

In spite of good work,
there are failures....

[Figure 3.2]

SELECTED SETBACKS FIRST QUARTER 2004

COMPANY	PRODUCT	INDICATION	FAILURE STAGE (DATE)
Millennium Pharmaceuticals	VELCADE	Colorectal Cancer	Phase II (Jan-04)
InterMune	Actimmune	Idiopathic Pulmonary Fibrosis	Phase III (Jan-04)
AstraZeneca	IRESSA	Glioblastoma	Phase II (Jan-04)
Neurogen	NGD 2000-1	Asthma	Phase IIa (Jan-04)
ILEX Oncology	Eflornithine	Superficial Bladder Cancer	Phase III (Jan-04)
InterMune	Interferon Gamma-1b	Advanced Cirrhosis	Phase II (Jan-04)
Labopharm	Tramadol	Pain Relief	*Phase III (Jan-04)
Schering AG	Ad5FGF-4	Stable Exertional Angina	Phase IIb/III (Jan-04)
Human Genome Sciences	KGF-2	Induced mucositis	Phase II (Feb-04)

Schering-Plough Cortex Pharma/	SARASAR CX516	NSCLC Mild Cognitive Impairment	Phase III (Feb-04) Phase II (Feb-04)
Les Laboratoires			
Pfizer	DK-507k	Infectious Disease	Phase I (Feb-04)
Stressgen	HspE7	Anal Dysplasia	Phase III (Feb-04)
Seikagaku	SI-7201	Interstitial Cystitis	NA (Mar-04)
Chiron	Tezacitabine	Gastroesophageal Cancer	Phase II (Mar-04)
Genentech/XOMA	RAPTIVA	Psoriatic Arthritis	Phase II (Mar-04)
Myogen	EMOTE	Chronic Heart Failure	Phase III (Mar-04)

* Statistical significance not achieved in 1 of 3 studies.

Source: Burrill & Company

Product Characteristics

- 65-70% of products will be an injectable formulation (protein-based)
 - Demand for refrigerator/freezer capacity
 - Product shelf life – inventory management
 - Availability issues almost assured
 - Patient instruction for administration/reimbursement
- Patient-specific tissue-derived products
 - Express handling
 - Safety / hazmat concerns
 - Timeliness of delivery

Impact on Pharmacy

- Continued growth in physician and institutional administration of biotech products—pending reimbursement policy—watch Medicare Part B for future trends
- Specialty services
 - HIV / AIDS
 - Oncology
 - Rheumatology
- Need to create model to manage products that have high-risk, are in short supply, have short shelf life and be non-returnable
- Alternative delivery systems have arisen from uniqueness of treatments

Alternative Distribution Systems:

Two distinct functional capabilities emerging for product distribution

- predictable demand, highly efficient
- 80% of market
- innovations or other unique handling, use requirements
- 20% of market

Key: Knowing which is needed

Emergence of Two Supply Chains*

	Primarily Functional Product	Primarily Innovative Product
Efficient Supply Chain	Match	Mismatch
Responsive Supply Chain	Mismatch	Match

- **Important for manufacturers to understand their product characteristics in order to select correct one**

* Fisher, M.L. "What is the Right Supply Chain for Your Product?", Harvard Business Review, March-April 97, page 105-116.

Goals by Product Type

- Functional Products: focus on cost reduction
- Generally, price-sensitive, low-margin
- MRP Software: minimize inventory & maximize production efficiency
- Flow of information between manufacturer, distributor, retailers key

Goals by Product Type

- Innovative Products: Focus on market mediation costs
- Read market and move product where demanded
- Early sales tracking & other market signals
- Information flow within chain and the marketplace

Early Examples Rx Industry

- Hivid: market responsive product launch—open distribution
- Crixivan: market responsive product launch—restricted distribution

Physically Efficient vs. Market-Responsive Supply Chains

Physically Efficient Process

Market-Responsive Process

Primary purpose

Supply predictable demand efficiently at the lowest cost

Respond quickly to unpredictable demand in order to minimize stockouts, forced markdowns, and obsolete inventory

Manufacturing focus

Maintain high average utilization rate

Deploy excess buffer capacity

Inventory strategy

Generate high turns and minimize inventory throughout the chain

Deploy significant buffer stocks of parts or finished goods

Lead-time focus

Shorten lead time as long as it doesn't increase costs

Invest aggressively in ways to reduce lead time

Approach to choosing suppliers

Select primarily for cost and quality

Select primarily for speed, flexibility and quality

Product -design strategy

Maximize performance and minimize cost

Use modular design in order to postpone product differentiation for as long as possible

Is it Happening in Rx Industry?

- Growth of 3PLs and specialty distributors in past 10 years
- Manufacturers accustomed to using traditional distribution have difficulty understanding requirements of new products at times
- New manufacturers may make mistakes as documentation in Rx industry of two systems relatively recent—6 years

Impact of Biotechnology

- Have shed light on reality of two supply systems existing
- Different systems to manage biotech drugs, now commonly known as “specialty” products
- Some new products carry high risk with no system to manage: Clozaril early example of closed distribution system development
- FDA studying pharmaceutical risk management programs, may further impact community pharmacy

Impact: Finance

- Distributors & Pharmacy
 - Accounts Receivable - longer cycles tied to longer reimbursement claims processes
 - Higher cost products, assume more liability and greater potential loss for default
- Payors
 - Moving injectables from medical to pharmacy budget; greater scrutiny of these products; greater demand for outcomes tied to high acquisition cost
 - Establishing a fourth tier for high tech, biotech, self-injectable and gene therapy
 - Will they pay? Will consumers make them? Covenants for patient responsibility?

Specialty Drug Spend Trends*

Exhibit 17

Specialty Drug Trend 2001 to 2003

Year	PMPY Rxs	Trend	Avg Cost per Rx	Trend	PMPY Cost	Trend
2001	0.014	N/A	\$1,091.40	N/A	\$15.44	N/A
2002	0.020	44.5%	\$1,193.90	9.4%	\$24.42	58.1%
2003	0.028	35.3%	\$1,223.59	2.5%	\$33.87	38.7%

* From Express Scripts 2003 Drug Trend Report

Specialty Drug Spend Trends*

Top Five Specialty Drugs 2003

Brand Name (Approval Date)	PMPY Cost	Indication	Main Competitor(s) (Approval Date)
Enbrel® (1998)	\$5.40	Rheumatoid Arthritis	Humira™ (2002)
Rebetol® (2001)*	\$2.60	Hepatitis C	COPEGUS® (2002) Ribasphere™ (2004) ribavirin (2004)
Copaxone® (1997)	\$2.37	Multiple Sclerosis	Betaseron® (1993) Avonex® (1996) Rebif® (2002)
PEG-Intron® (2001)	\$2.08	Hepatitis C	Pegasys® (2002)
Procrit® (1990)	\$1.70	Anemia	Epogen® (1989) Aranesp™ (2001)
Other	\$16.11		
Total	\$33.87		

* Although Rebetol has been approved since 1998 as part of the combination product Rebetron®, it was not approved by the FDA as a separate drug until 2001. Generics were launched in 2004.

Emerging Pharmacist's Role...

- Manufacturers make drugs, pharmacists make drugs work
- More accurately: pharmacists help patients "make drugs work", because the patient is the ultimate risk manager
- Or not...and drug-related morbidity and mortality results
 - Significant cost, >\$177 billion
- Or not...and products are withdrawn or use is limited
 - Cisapride
 - Bromfenac
 - Troglitazone

What Are Pharmacists Doing?

- Changing focus from order fulfillment to patient care
 - Prescriptions dispensed v. patients evaluated
- Providing patient education
- Monitoring medication use
 - Tracking compliance
 - Documenting patient progress, adverse events
- Confirming and document compliance with product restrictions
 - Performing testing
 - Documenting completion of testing



See the future...

- Systems being developed to manage products with specific risks
- Maximize pharmacist contribution
- Secure ability to play in new systems
- Improve medication use, maximize the benefits

How Can You Prepare?

- Position yourself as knowledge broker: Biotech shows great opportunity but often pharmacists left out
- Read all you can on biotechnology and medicine: Nature 4/2003 and www.bio.org
- Help educate public about biotech contributions
- Basic knowledge and educate staff at all levels of organization and your constituents

Resources

- www.fda.gov: pipeline and approvals
- www.pharmalive.com: pipeline database
- www.bio.org: meds in development
- www.burrilldatacenter.com--the "IMS of Biotech" Burrill & Company
- Future studies: CE, LLC

How Can You Prepare?

- Keep up with FDA's Risk Management Program development: JAPhA Nov/Dec 2001 Supplement and www.fda.gov. FDA Concept Paper and 4/2003 public meeting....stay tuned.
- Create capacity to store, distribute and administer immunizations--vaccines!!
- Inventory/Buying Groups: Build contingency plans based on air travel disruptions: how much needs to be close to point of care via ground transport?
- Role of "home" delivery? Especially since it's important to customers and drives satisfaction. Can also position you against home care-type specialty distribution

How Can You Prepare?

- Build skills and transfer across non-traditional disease states e.g. inhaled insulin in diabetes vs. inhalers for asthmatics
- Build on collaborative relationships that put patient in center--much will be administered MD office but managed by pharmacy
- 5 years: genomic tests the domain of primary care doctors while pharmacists recommend appropriate therapy--how to parlay pharmacy Rx care programs? Assay tests for individualized therapy.

How Can You Prepare?

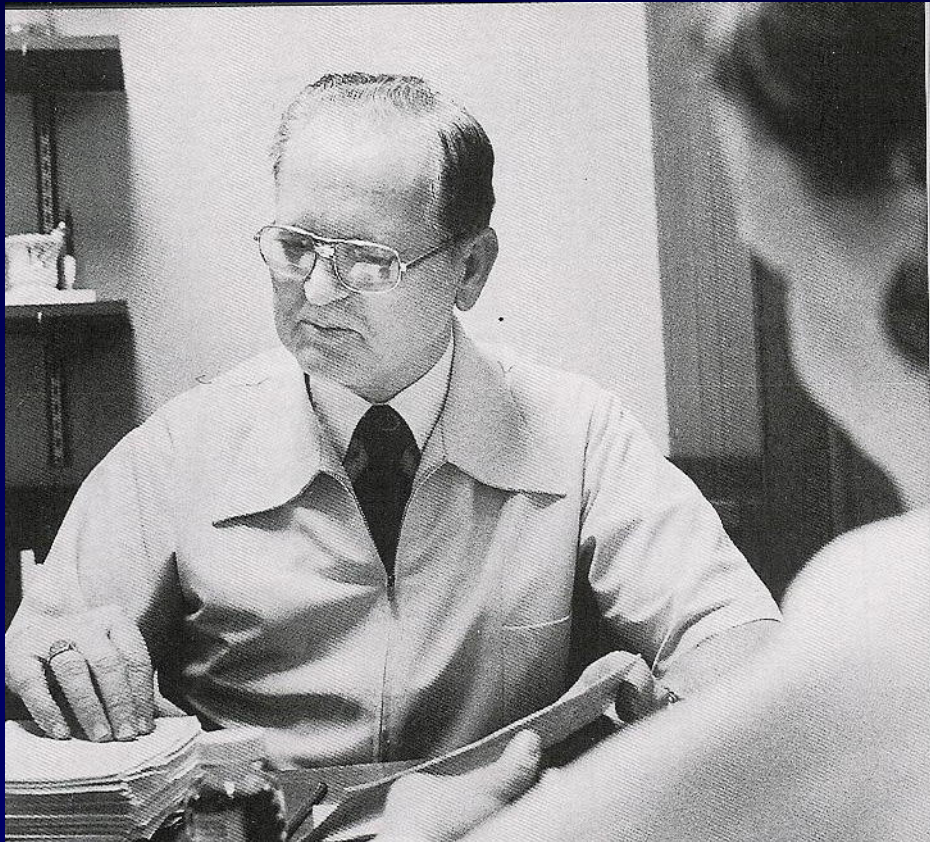
- Create model to manage products that have high-risk, are in short supply, have short shelf life and be non-returnable
- Explore performance-based networks and other specialty networks and consider joining one
- Make your voice heard on distribution system issues like these with your state and national associations, FDA and manufacturers who implement programs
- Consider proactively education manufacturer representatives. Invite them to your practice to see how current controlled distribution and risk management programs actually impact operations and patient care
- Think of other action steps you can take that will keep you part of this new environment. Share them with your peers.

How Can You Prepare?

Access Monies for Innovation:

- www.iacp.com
 - Laura Cranston
 - \$5 million per year
- www.communitypharmacyfoundation.com
 - Lou Sesti
 - \$750,000-\$1million per year
- www.aphafoundation.org
 - Bill Ellis
 - \$20K per year
- HRSA & CMS--demonstration grants

What Other Ideas Do You Have?



It's not an easy path...but remember:

If you want a rainbow, you
have to put up with the
rain.

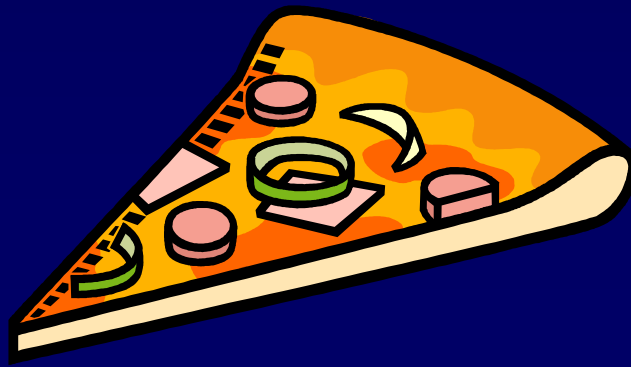
Dolly Parton

Life is like pizza. Even when
it's bad, it's good.

Paula Devico



Shiprock & Rainbow
Navajoland, Arizona
G. Arnell Williams: www.dramainnature.com



Thanks for Having Me!

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