基因药物研发及产业动向

The R&D of Gene Drugs in China, Today and Tomorrow

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Summary

- Current Status of R&D
- R&D Examples:
  - Responsive R&D
  - Breeding R&D
  - Source R&D
- Need to Develop Public Technology Platform for Research
- Patent
- R&D Opportunity in China
- Development Trend in the Industry

What is Genetic Medicine?

Genetic Medicine is: bio-based active material product based in functional gene or genetic outcome found in genomic research, produced with genetic technology including Biology, Molecular Biology, Biochemistry, BioProcess Engineering. Genetic Medicine controls the quality of finished products and intermediate products and is used in clinical treatment, prevention and diagnostic treatment of diseases .

Comparison between Genetic and Small Molecule Medicine

Small Molecule Medicine	Genetic Medicine
Organic compounds through chemical synthesis	Protein or carbon compounds in living organisms
Molecular weight MW < 5 KDa	Molecular weight MW > 5 kDa
Active to animals of many kinds	Active to responsive animals
Act on the target directly	Relative to complex, temporary doses
peculiar action mechanism	Much genetic effect
Short duration	Long duration
Disappear through metabolism	Enzyme hydrolysis
Induce toxicity due to hereditary compounds or metabolic results	Pharmacologic mechanism
Stable, heat-insensitive	Unstable, heat-sensitive, easy to polymerize

Types of Genetic Medicine

- Growth Factor, Colony Stimulating Factor, Polypeptid Hormone
- Interferon, Interleukin
- Recombination Human Monoclonal Antibody
- Genetic Therapy
- Nuclear Adic: DNA, Complimentary RNA, SiRNA
- Vaccine (protein recombination, DNA vaccine)

Approved Genetic Medicine

	US	EU	others
• **Protein Recombination drug:**	**39**	**38**	**46**
• **Antibody Recombination drug:**	**18**	**13**	**6**
• **Nuclear acid Likeness:**	**4**	**0**	**3**
• **Recombination Vaccine:**	**3**	**5**	**4**

World Top 5 Genetic Medicine in 2003 and 2004

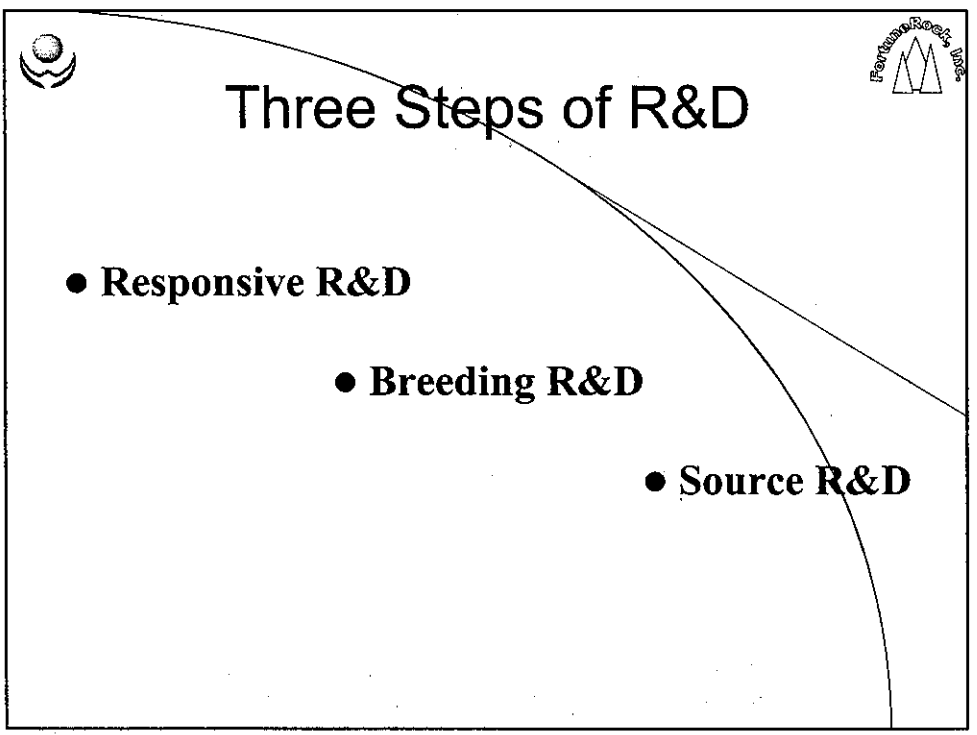
Rank	Class	Sales (US billion)	Efficacious disease	Release time	Major Producer
1	EPO	81/106*	Anemia	1989	Amgen, J&J, Ortho
2	IFN-α -β	28.9 27.7	Cancer, Hepatitis C	1986	Schering-Plough, Roche, Serono, Bioen
3	Insulin	42.6	Diabetes	1982	Eli Lilly, Novo
4	G-CSF	35	Neutral particle cell disease, Leukemia, HIV/AIDS	1991	Amgen
5	rhGH	20	Growth disorder	1987	Pharmacia, Serono, Genentech, Eli Lilly, Novo
	Total	235.2			

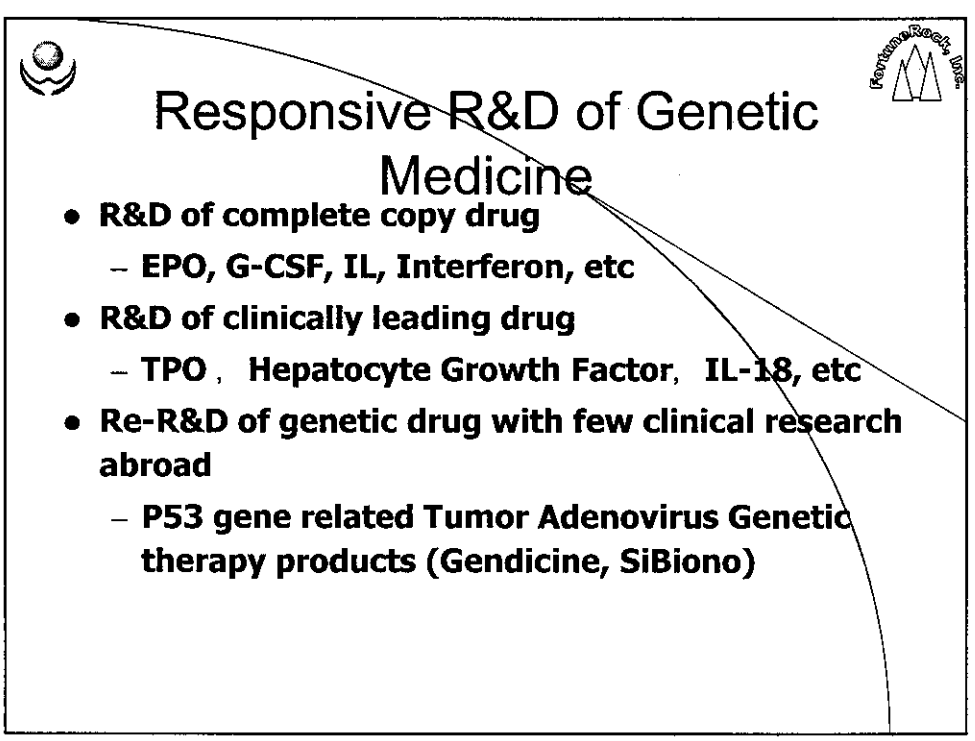
* Sales in 2004

Total sales of biotech product: $48 billion
Total sales of genetic medicine:$33.6 billion

Crucial and Urgent Technical Problems in R&D

- To secure independent Intelligence Property Right through strengthening source research
- To secure the competitive edge through development of Core Technology and Public Platform Technology
- R&D of Breeding Genetic Drug is the breakthrough in Chinese biotech pharmacy


Three Steps of R&D
Responsive R&D
Breeding R&D
Source R&D


Responsive R&D of Genetic Medicine
R&D of complete copy drug
– EPO, G-CSF, IL, Interferon, etc
R&D of clinically leading drug
– TPO , Hepatocyte Growth Factor, IL-18, etc
Re-R&D of genetic drug with few clinical research abroad
– P53 gene related Tumor Adenovirus Genetic therapy products (Gendicine, SiBiono)

Breeding R&D of Genetic Drug

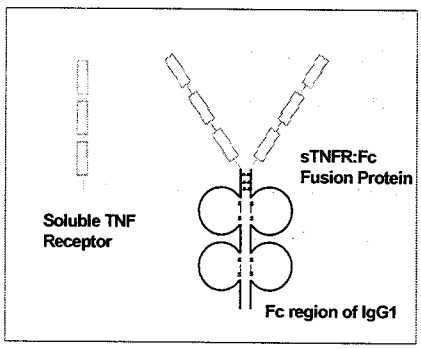
- **Chemical Protein Formula Medicine**
  - **PEG formula, Lipid-embeded**
- **Recombination Deformed Protein Medicine**
  - **Rapid-acting, long-lasting Insulin: long-lasting EPO**
- **Recombination Human Monoclonal Antibody**
- **Recombination Fusion Protein Medicine**
  - **IgG (Fc)**
  - **Receptor**
  - **HSP (*CoVal*)**
  - **HSA**

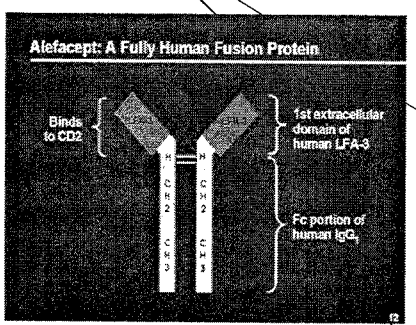
Recombination Deformed Protein Medicine

Insulin and Erythropoietin

- **Rapid-acting Insulin**：
  - **Humalog （B29/B28) (Eli Lilly)**
  - **Novolog (ProB28Asp) (Novo Nordisk)**
- **Long-lasting Insulin**：
  - **Lantus (Three AA changes) (Aventis Pharma.)**
  - **Detemir/NN304 (B30del/B29 fatty acid) (Novo Nordisk)**
- **Long-lasting Erythropoietin**
  - **Aranesp （Amgen)**

Recombination Fusion Protein Medicine-IgG/Receptor

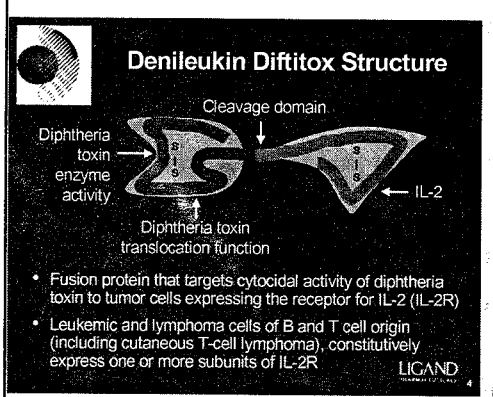


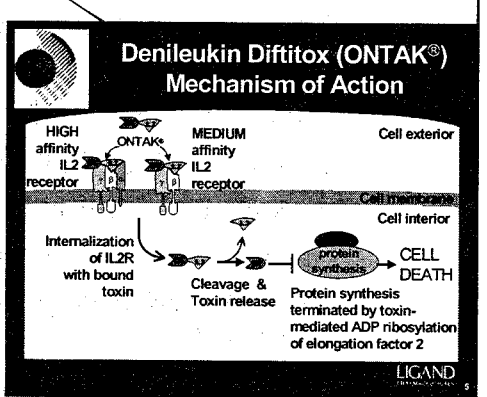


ENBREL/etanercept (Amgen/Wyeth) 01/2002

AMEVIVE/alefacept (Biogen,Inc.) 02/2003

Recombination Fusion Protein Medicine – human/non-human protein





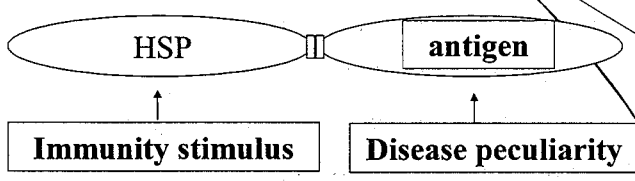
ONTAK/Denileukin diftitox Seragen, Inc. 02/1999

·Fusion Protein of Diphtheria Toxoid piece A,B and human Interleukin-2

·Treats lymphoma of T cell

Recombination Fusion Protein Medicine-HSP

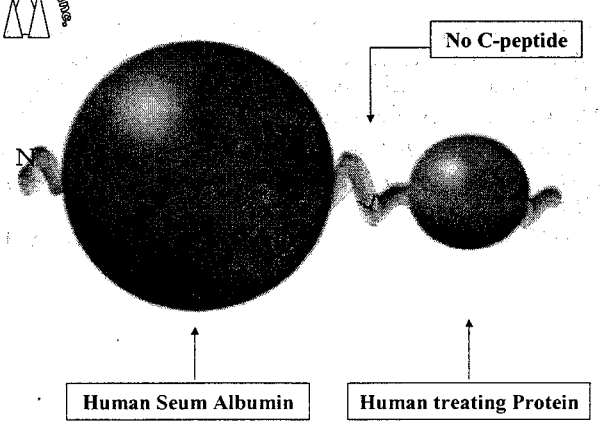
From: Stressgen Biotechnologies Corp.
CoVal fusion protein technoloy platform



Heat Shock Protein and an antigen form fusion protein to treat cancers, immune deficiency diseases and infectious diseases.

HspE7 (for HPV) already is going through the approval process of FDA.

Recombination Fusion Protein Medicine-HSA



Recombination Fusion Protein Medicine – HSA

- FortuneRock, Inc.: Albugen-CPSFs,
  - Albugen platform technology product : long-lasting EPO, long-lsting ILs, long-lasting Interferons, long-lasting TPO, etc
- Human Genome Sciences Inc.:
  - Albuferon-Alpha, Albuleukin, Albutropin, Albugranin
- Delta Biotechnology Ltd.: Albfuse™
- Chinese Academy of Military Medical Sciences
  - HSA/GCSF, HSA/IFN-α

Recombination Fusion Protein Medicine-HSA

- **50% of protein in blood is human Serum Albumin**
- **Serum Albumin is globular and non-glycosylated protein**
- **Carrier to various structures in blood. Ex) protein, hormone, fatty acid, steroid, small molecule compounds, etc**
- **Important blood stabilizer and reproducer**
- **Important excipient and stabilizer for most protein drug**
- **Fusion Protein doesn' t include any type of foreign polypeptide**
- **Ex) long-lasting Interferon, long-lasting EPO, long-lasting Inerleukin**

Adenovirus Carrying Gene Therapy Medicine

Substantial Tumor Treating Tenetic Medicine

- Genetic Therapy Medicine for Human p53 Adenovirus (Shemzhen SiBiono GeneTech Co., Ltd.)
- Genetic Therapy Medicine for Anti-tumor Adenovirus (Shanghai Sanwei Biotech Co., Ltd.)
- Genetic Therapy Medicine for KTV serises Human Rb or Rb2 adenovirus (Tianfin Fuying Co., Ltd.)
- Genetic Therapy Medicine for Human p16 Adenovirus (Shemzhen Taitai Genomics, Inc.)

Development of Source Genetic Medicine

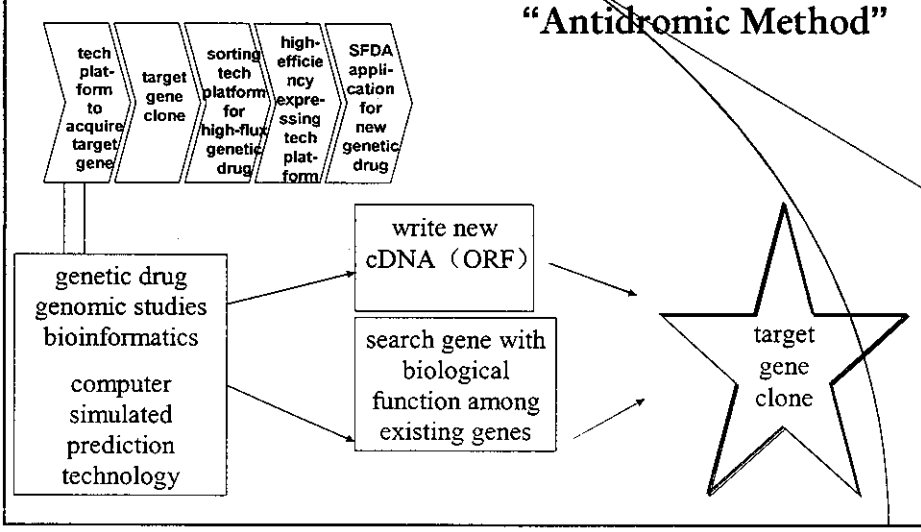
- **Find New gene with bio function**
- **Add new bio function to the already known gene**

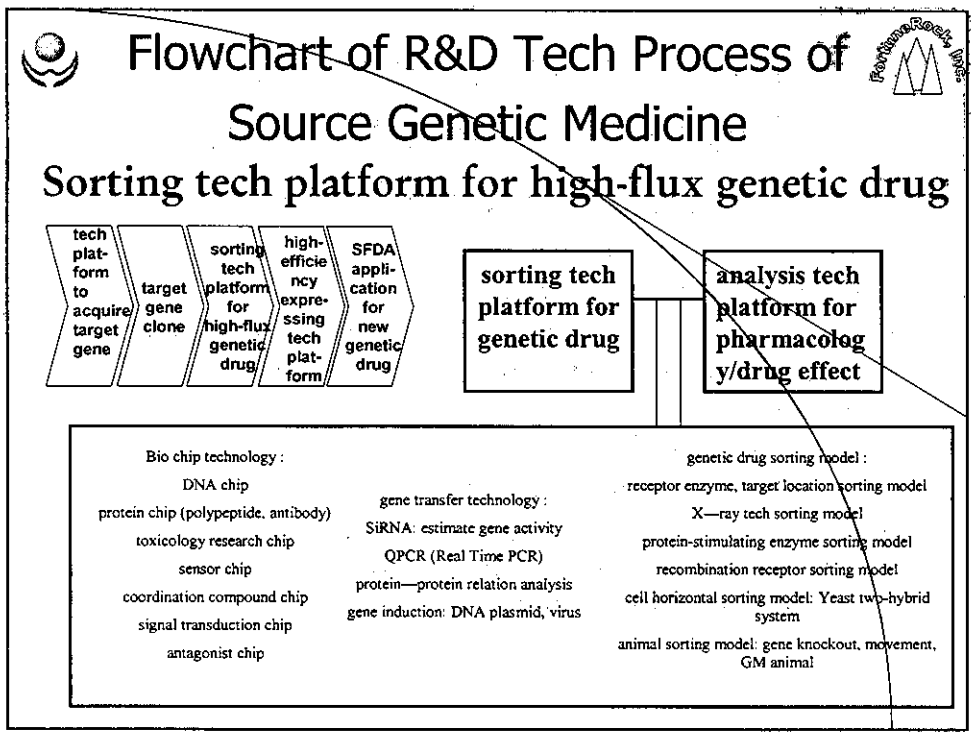
Functional Genomic Research of Gene Drugs

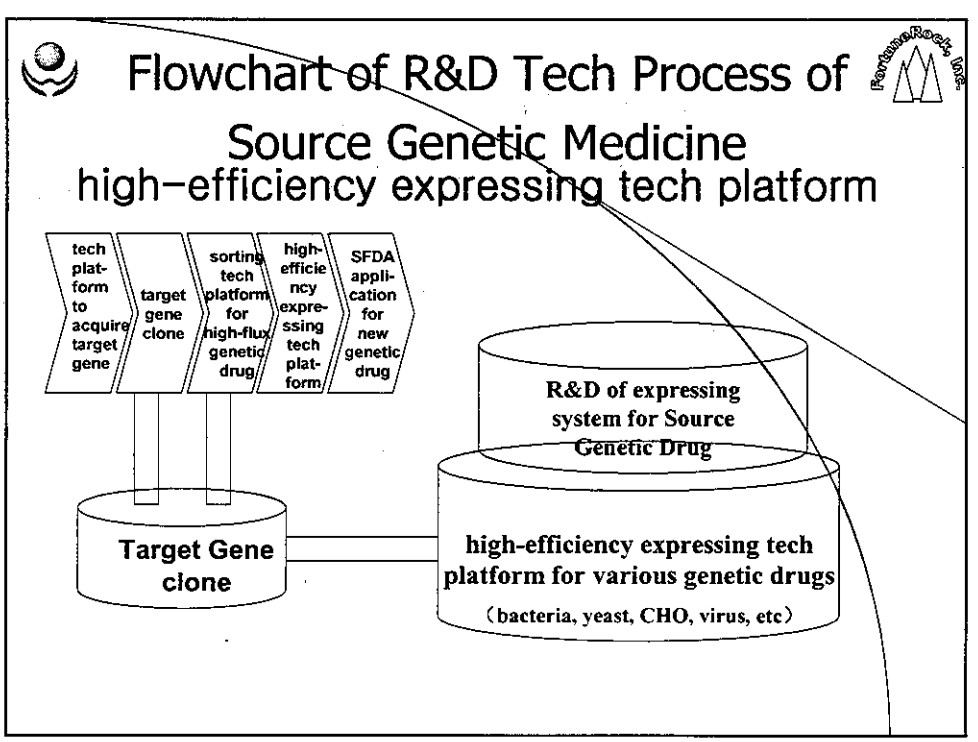
- Scientific background study/summary of literatures
- Use bioinformatic approaches to identify novel genes
- Disease relevance/hypothesis
- Competitive landscape
- Key decision points
- Experimental design
- Short and long term plans

Flowchart of R&D Technology Process of Source Genetic Medicine

technical platform acquiring target gene by "Antidromic Method"




Flowchart of R&D Tech Process of Source Genetic Medicine
Sorting tech platform for high-flux genetic drug
tech plat-form to acquire target gene
target gene clone
sorting tech platform for high-flux genetic drug
high-efficie ncy expre-ssing tech plat-form
SFDA appli-cation for new genetic drug
sorting tech platform for genetic drug
analysis tech platform for pharmacolog y/drug effect
Bio chip technology :
DNA chip
protein chip (polypeptide, antibody)
toxicology research chip
sensor chip
coordination compound chip
signal transduction chip
antagonist chip
gene transfer technology :
SiRNA: estimate gene activity
QPCR (Real Time PCR)
protein—protein relation analysis
gene induction: DNA plasmid, virus
genetic drug sorting model :
receptor enzyme, target location sorting model
X—ray tech sorting model
protein-stimulating enzyme sorting model
recombination receptor sorting model
cell horizontal sorting model: Yeast two-hybrid system
animal sorting model: gene knockout, movement, GM animal


Flowchart of R&D Tech Process of Source Genetic Medicine
high-efficiency expressing tech platform
tech plat-form to acquire target gene
target gene clone
sorting tech platform for high-flux genetic drug
high-efficie ncy expre-ssing tech plat-form
SFDA appli-cation for new genetic drug
R&D of expressing system for Source Genetic Drug
Target Gene clone
high-efficiency expressing tech platform for various genetic drugs
(bacteria, yeast, CHO, virus, etc)

Research Needs for Public Technology Platform of Genetic Medicine

- The trend of drug research is toward longer lasting drug in the body
- The most ideal existing technique is to realize durability of genetic drug's effect through recombination technology
- The high efficiency express tech is critical in producing recombination protein drug
- The trend of recombination protein drug research is inevitably toward the long-lasting recombination protein drug

Developments in Chinese Genetic Medicine Industry

- Human Resources：very qualified and quantified
- Facility：standardized construction of GMP workshops
- Target Disease：cardiovascular diseases, diabetes, cancers, infectious diseases
- Performance & Development: more than 40 type of products released
- Issues to be taken carefully in the development process:

  High Technology！Vigorous Investment！

  High Risk！Big Profit！