Gene therapy

Lecture Plan

1. Molecular Medicine and Gene Therapy: An Introduction
2. Vectors in Gene Therapy
    1. Viral vector of gene therapy
    2. Non viral vector of gene therapy
3. Gene Targeting
4. Cancer genes and the pathways they control
5. The Genetic Basis of Cancer
6. Gene therapy progress and prospects cancer
7. Tumor Suppressor Gene Replacement for Cancer
8. Antisense Technology
9. Receptor directed molecular conjugates for gene transfer
10. Conditional gene targeting for cancer gene therapy
11. Pharmacogenetics of breast cancer therapies
12. Hypoxia targeting gene expression for breast cancer gene therapy
13. Gene expression profiling: Decoding breast cancer
14. Ethical issues in Molecular Medicine and Gene Therapy
15. Epilogue: Personal Genetic Medicine—The Future Is Now
16. Term paper: Commercial Implications of gene therapy

Molecular Medicine and Gene Therapy

Segment: 1

Gene Therapy

Here are some things you'll want to think about.

If you want to develop a cure for a disease by gene therapy, here are some things to think about:

- How will you reach the target cells and deliver the gene?
  - ex vivo vs. in vivo
- What proportion of target cells need to be altered?
- Does the gene need to be expressed constitutively, or regulated?
- Would there be serious consequences if the gene were overexpressed?
- How long will the DNA persist and be expressed?
- If you are planning to modulate gene expression, how will you do it (e.g. ribozymes, antisense, short interfering RNAs ! siRNA)?

Some Diseases

TABLE 1.1 Selected Inherited Disorders and Their Genetic Basis

Classification	Nomenclature	Characterization	Frequency
Autosomal aneuploidies newborns	Trisomy 13	Karyotype: 47,XX or XY +13 (extra copy)	1 per 12,000
	Trisomy 18	Karyotype: 47 XX or XY +18 (extra copy)	1 per 6000 newborns
	Trisomy 21 Down's syndrome	Karyotype: 47,XX or XY +21 (extra copy)	1 per 800 newborns ↑ incidence with age
Sex chromosome aneuploidies	Klinefelter's syndrome	Karyotype: 47, XXY plus variants	1 per 700 newborns males
	Triple X female	Karyotype: 47,XXX	1 per 1000 newborns
	Turner's syndrome	Karyotype: 45,X; 45X/46XX or 45X/46XY	1 per 1500 newborn females
	XYY male	Karyotype: 47,XXY	1 per 800 newborns
Autosomal dominant	Aniridia, type I	Chromosome 2 defect	1 per 80,000
	Aniridia, type II	Chromosome 11 defect	1 per 80,000
	Polycystic kidney disease	Chromosome 16 linkage	1 per 1250
	Charcot–Marie–Tooth	Two forms type I and II	1 per 2800
	Familial polyposis coli and Gardner's syndrome	Chromosome 5; adenomatous polyposis coli (APC) gene	1 per 8000
	Huntington's disease	Linked to chromosome 4p	1 per 3000
	Intrahepatic cholestasis	Vanishing bile ducts	
	Alagille syndrome	*Jagged 1* gene—20p12	1 per 70,000 familial
	Byler's disease	18q21	
	Marfan's syndrome	Chromosome 15: FBN1 gene	1 per 20,000
	Myotonic dystrophy	19q13.2–q13.3	1 per 8000
	Neurofibromatosis		

Ref: An introduction to molecular medicine and gene therapy 2001

TABLE 1.1 (*Continued*)

Classification	Nomenclature	Characterization	Frequency
	Idiopathic	SPINKI-Chromosome 5 Missense mutation- N345	
Autosomal recessive	α_1-Antitrypsin deficiency	Chromosome 14 Multiple alleles based on phenotype M, S, Z, I	1 per 3500
	Cystic fibrosis	7q31–q32, CFTR gene Multiple alleles: Δ 508 ↑ Also R117H, R75Q, D1270N	1 per 2500 (Caucasians)
	Gaucher's disease Ashkenazic Jewish descent	N370S allele (nonneuropathic)	1 per 625
	Caucasian population	L444P allele neuropathic	
	Hemochromatosis	HFE gene C282Y and H63D mutations	1 per 300
	Thalassemia (α)	Globulin gene complex on chromosome 16 Two alles α-thal 1 α-thal 2	1 per 250–1000
	Thalassemia (β)	Chromosome 11 Two alleles β(+) IVS-I β(+) IVS-II	

Ref: An introduction to molecular medicine and gene therapy 2001

More common disorders

Disorder	Mutation	Chromosome
22q11.2 deletion syndrome	D	22q
Angelman syndrome	DCP	15
Canavan disease		17p
Celiac disease		
Charcot-Marie-Tooth disease		
Color blindness	P	X
Cri du chat	D	5
Cystic fibrosis	P	7q
Down syndrome	C	21
Duchenne muscular dystrophy	D	Xp
Haemochromatosis	P	6
Haemophilia	P	X
Klinefelter's syndrome	C	X
Neurofibromatosis		17q/22q/?
Phenylketonuria	P	12q
Polycystic kidney disease	P	16 (PKD1) or 4 (PKD2)
Prader-Willi syndrome	DC	15
Sickle-cell disease	P	11p
Tay-Sachs disease	P	15
Turner syndrome	C	X

P -

Point mutation, or any insertion/deletion entirely inside one gene

D -

Deletion of a gene or genes

C –

Whole chromosome extra, missing, or both - see chromosomal aberrations

T –

Trinucleotide repeat disorders - gene is extended in length

www.wikipedia.com

Monogenetic Disorder

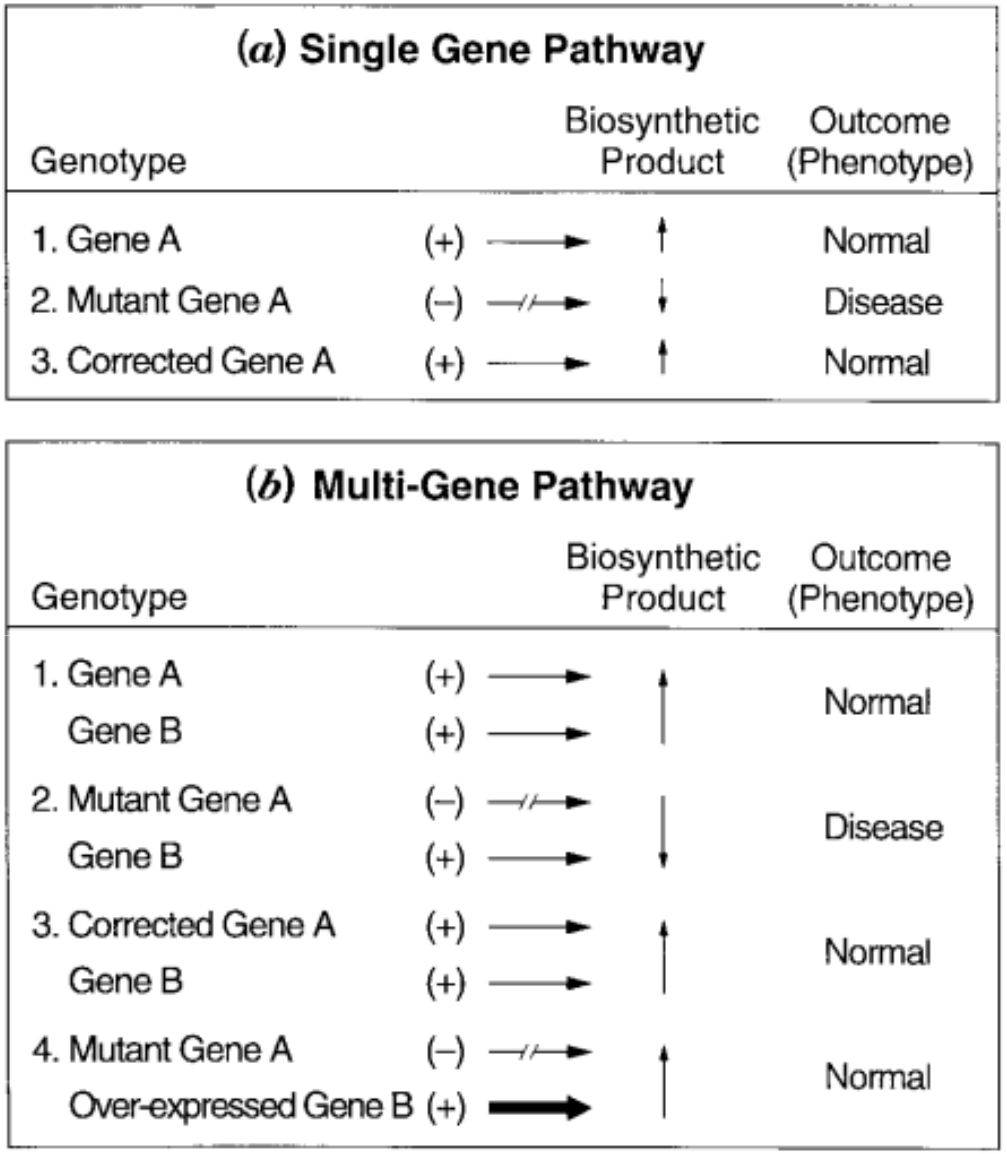
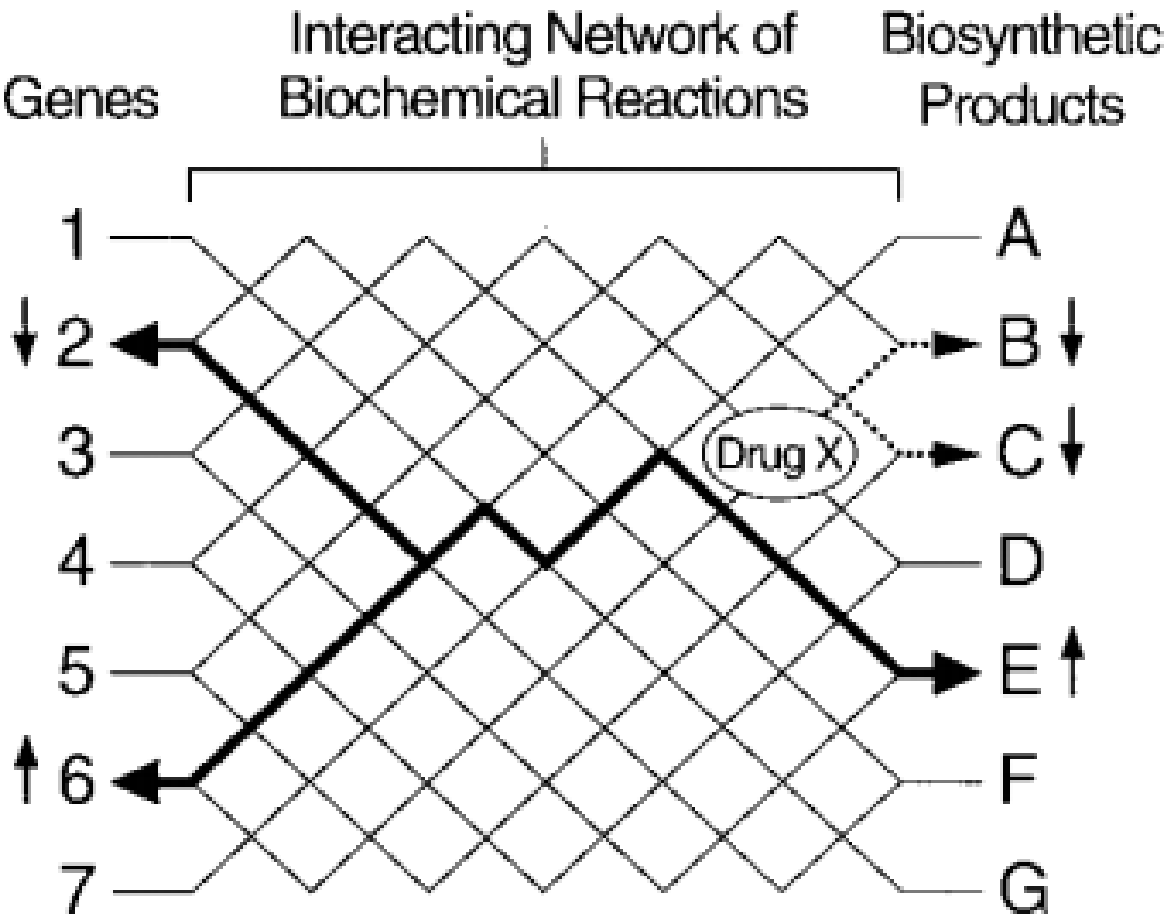


FIGURE 1.1 Pathology can result from a single gene defect, as illustrated in (*a*). More often, multiple genes are involved. In the latter case, a variety of gene therapy options may exist, as depicted in (*b*).

Ref: An introduction to molecular medicine and gene therapy 2001

Schematic representation of a system in which genotype and phenotype Are related by a complex network of interaction involving many proteins, RNA and reactants



Ref: An introduction to molecular medicine and gene therapy 2001

Ethics and Regulation

Guidance, Compliance & Regulatory Information (Biologics)

Biologics Guidances

Cellular & Gene Therapy Guidances

Resources for You

- Consumers (Biologics)
- Healthcare Providers (Biologics)
- Industry (Biologics)
- About the Center for Biologics Evaluation and Research

Cellular & Gene Therapy Guidances

Search Guidance

go

We have recently redesigned the FDA Web site. As a result, some Web links (URLs) embedded within Guidances, Rules and other documents are no longer valid. If you find a link that does not work, please try searching for the document using the document title. For more assistance, go to Contact FDA.

Cellular & Gene Therapy Guidance Documents

- Guidance for Industry: Cellular Therapy for Cardiac Disease
  October 2010. (This guidance finalizes the draft guidance entitled "Guidance for Industry: Somatic Cell Therapy for Cardiac Disease" dated March 2009 (April 2, 2009, 74 FR 14992).
- Assay Development for Immunogenicity Testing of Therapeutic Proteins (PDF - 161KB)
- Draft Guidance for Industry and FDA Staff - Investigational New Drug Applications (INDs) for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications (PDF - 91KB)
  10/2009
- Guidance for Industry - Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications (PDF - 462KB)
  10/2009
- Draft Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines
  9/2009
- Guidance for Industry: Considerations for Allogeneic

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Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events

[PDF version]

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov /cber/guidelines.htm.

For questions on the content of this guidance, contact the Office of Cellular, Tissues, and Gene Therapies at 301-827-5102.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2006

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Guidance, Compliance & Regulatory Information (Biologics)

Biologics Guidances

Cellular & Gene Therapy Guidances

Resources for You

- Federal Register Notice: Guidance for Industry: Cellular Therapy for Cardiac Disease

Guidance for Industry: Cellular Therapy for Cardiac Disease

[PDF Printable Version - 200 KB]

This guidance finalizes the draft guidance entitled "Guidance for Industry: Somatic Cell Therapy for Cardiac Disease" dated March 2009 (April 2, 2009, 74 FR 14992).
Document Issued on: [October 2010]

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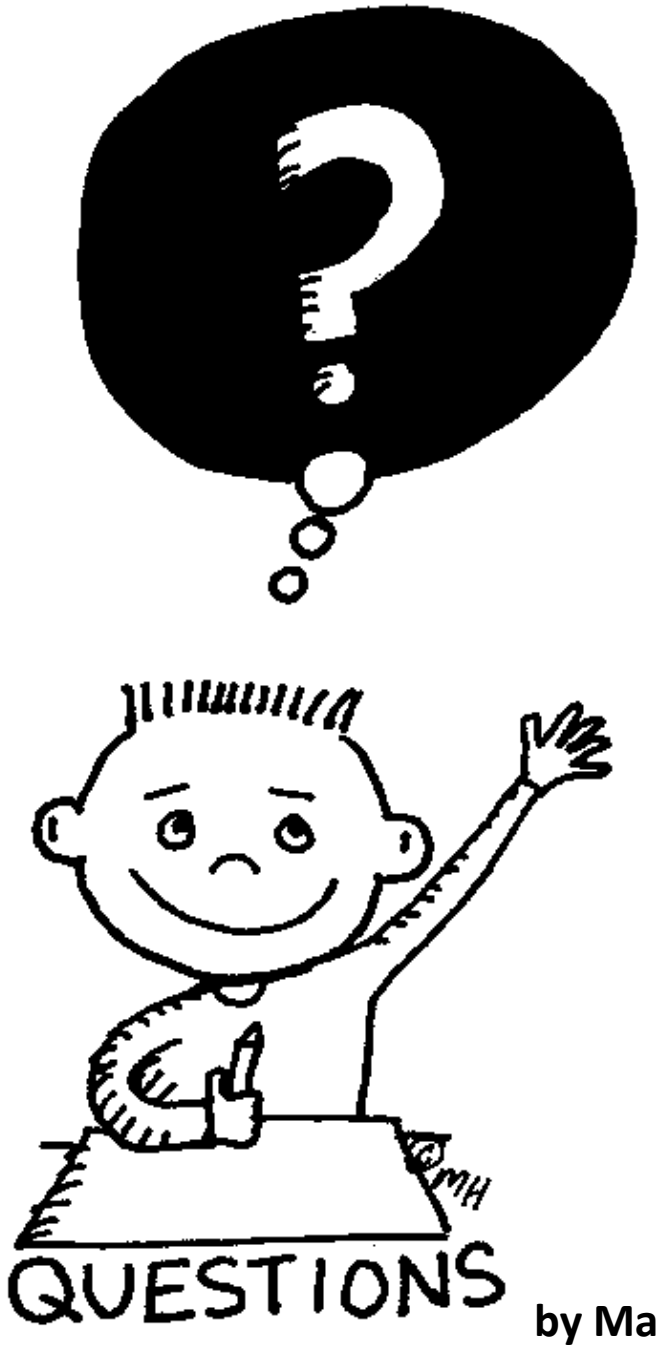

by Mark A. Hicks, illustrator.