GREAT STRIDES IN SCIENCE … WHAT ABOUT ACCESS?

Marlene E. Haffner, MD, MPH
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1982 – WHAT HAS HAPPENED SINCE IN TECHNOLOGY ASSESSMENT AND....

- US Orphan Drug Act Passed - first in the World
- No universal Healthcare in the US
- Biotech only mildly beginning
- Dolly the cloned sheep had not yet been born (born in 1996)
- AIDS did not exist
- Hepatitis B vaccine approved 1982
ADVANCES IN HEALTH TECHNOLOGY SINCE 1982

Orphan Drug Designations and Approvals lead the way in the development of:

- Pegylation
- Liposomal encapsulation
- Gene therapy
- Immune modulators
- Cholesterol metabolism
- Biotechnology
- First treatment of HIV - AZT
PEGYLATION

• First used for adenosine deaminase (ADA) deficiency – PEG ADA
  • Clinical trial in 10 patients
  • A very “orphan disease”

• Definition / Why it worked / Advantages
  • Decreased degradation by metabolic enzymes
  • Decreased immunogenicity and antigenicity
  • Improve half-life of the protein

• Now broader use - eg - Pegasys and Peg-Intron for hepatitis C; also broad use in oncology settings
HISTORY OF GENE THERAPY

• First unapproved/unauthorized attempt at gene therapy
  • 1980
• Adenosine deaminase (ADA) deficiency
• OTC disease (ornithine transcarboxylase deficiency)
• First germline gene transfer (2001) – not FDA approved
• Promising results for Leber’s congenital amaurosis (LCA) (2012)
• Also studies in Hemophilia B and Sanfilippo (MPS IIIA)
• Glybera in the EU (2012) - approved but not yet marketed. Marketing expected 2015
GENE THERAPY

• The Dark Ages
  • 1980’s -1990’s – Negative outcomes (hemophilia, HIV)
    • Adenovirus (AdV)
      • Ornithine transcarbamylase (OTC)
      • Preexisting antibodies
    • Occurrence of malignancies

• The Come Back
  • AAV - Hemophilia
  • AAV Variant - Cystic fibrosis - deliver healthy genes to lung tissue
  • AdV
    • EBV lymphoma
    • Potentially neuroblastoma
  • Leber congenital amaurosis
  • Pancreatic Ductal Carcinoma
RISKS & BENEFITS

- Benefit will always have to outweigh the risk
- Stable gene insertion
- Concerns re mutagenesis
- Ethical Considerations
- Short lived effect in somatic cell Rx
- Potential immune response
- Will the vector “behave?”
- Unforeseen long term effects
- “Political considerations”
EFFECTIVENESS

• “Perfect Outcome” – Cure the disease
  • Somatic vs. germ line

• Influencing Factors
  • Improve duration of somatic cell therapy
  • Lack of Immune response
  • Safe Viral Vectors and new concepts of gene expression
    • liposomal
    • plasmid delivery systems
  • Accurate targeting
WHAT IS NEEDED FOR SUCCESSFUL GENE THERAPY?

• Suitable vector
• As much as it is a gene therapy it is also a cell therapy
• Avoiding Promoters
• Perfect Timing (how to make it last long enough to deliver and not get us sick-virus)
FDA
- Regulated by CBER - Office of Cell and Gene Therapy
- Extensive guidance re shedding of viral vector to alleviate any harm to others
- Other guidance
EU
- Gene therapy working party (GTWP)
- Multiple guidances
ICH Guidance
CORRELATION

• Orphan diseases frequently genetic

• Easier (perhaps) to study rare monogenetic diseases

• Most studies thus far have been in rare diseases
  • Hemophilia, Wiscott Aldrich, SCID, Lebers congenital Amaurosis, Metachromatic Leukodystrophy, CF, pancreatic CA

• Germ cell therapy will occur later, but rare diseases likely the first to be targeted
• 1980’s Biotech products almost impossible to achieve Personal Property Protection (Patent protection)

• 7 Year Orphan drug exclusivity imperative for Biotech drug development. Now have exclusivity in their own right

• Current situation considerably eased
IMMUNO MODULATORS

• First described in the 1980’s
• But current use still mainly in orphan diseases - malignancies
  • BCG for Bladder Cancer
  • Broader uses in Ulcerative Colitis, Rheumatoid Arthritis
• Remember Risk/Benefit
  • Potential for lymphoma
ANTIBIOTIC RESISTANT ORGANISMS

An increasing problem throughout the world

- TB, Gonorrhea, gram negative and gram positive organisms
- So far still an orphan situation; hopefully will remain that way depending on Regulation
ORPHAN PRODUCT SUCCESSES and ONGOING CHALLENGES

- Almost 600 products developed for orphan diseases in the US and EU combined
- Have the potential to treat many millions of patients + relieve the suffering of families of the patient
- Many diseases yet to be conquered
  - Need the science of the disease
- Natural History of the Disease remains paramount
- Must develop new paradigms of drug development to approach the lack of new products
  - Programs like BioPontis Alliance for Drug Development
  - Continuous manufacturing
ISSUES OF ACCESS TO ORPHAN PRODUCTS

COST
• Co-payment by the patient
• Refusal to pay by the Hospital/Insurance Company
• In the EU drugs are reimbursed on a member state by member state basis
• Is the Cost too high?
• What constitutes Cost
  • Poorly explained to the public
  • Economies of scale
• “Provider programs” by the sponsor - based on patient income

TIME FOR DRUG DEVELOPMENT
• Breakthrough therapy designation - eligible for all fast track features + organizational commitment of senior FDA managers
• Fast Track - based on unmet medical need
• Priority Review
• Accelerated Approval based on a surrogate endpoint
• EU - Qualification of novel methodologies for drug development: guidance to applicants
WHAT IS CURRENT THE STATUS

Many long strides have been taken on behalf of patients
But - the pace is too slow. New diseases being described every day. In the US an average of 30 - 40 new orphan drugs approved each year.

NEED
• Increased coordination between the US and EU
• New paradigms for development of therapies
• Gene Therapy will provide cures, but they are still mainly on the horizon
• Cost/access issues need to be better addressed
QUESTIONS

Marlene E. Haffner, MD, MPH
President & CEO
11616 Danville Drive
Rockville, Maryland 20852
http://www.mhaffner.com
mhaffner3@verizon.net
301 984 5729 (office)
301 641 4268 (cell)