GREAT STRIDES IN SCIENCE … WHAT ABOUT ACCESS?

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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
- No description of the Human Genome (1984 – 2003)
- 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)

Regulatory Stance
RISK VS BENEFIT

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

BIOtech PRODUCTS

- 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

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