

TO THINK BIOLOGICS...

***LEARNING FROM THE PAST,
DUTY FOR THE FUTURE***

Thoughts Through the Ages...

- ❖ **Natura enim non imperatur, nisi parendo:**
“Nature cannot be ordered about, except by obeying her”
 - ❖ **Novum Organum (1620), Sir Francis Bacon**
- ❖ **“...in nature there are no rewards or punishments; there are consequences.”**
 - ❖ **Some Reasons Why (1881), Robert Ingersoll**
- ❖ **For every intended consequence, there are a hundred mostly unknown unintended consequences that we must address...**
 - ❖ **FDA research-reviewer’s lament**

Tragedy to Action

- ❖ **13 children in St. Louis died of tetanus after receiving diphtheria antitoxin (1901) from a horse named Jim**
- ❖ **“This tragedy convinced Congress and the public that producing antitoxin or vaccine was not a simple matter like weighing out a dose of a drug on a scale.”**
 - ❖ **Margaret Pittman, “The Regulation of Biological Products, 1902-1970”**

Biologics Control Act of 1902

❖ “Although the preventive and curative powers of viruses, serums, toxins, antitoxins, and analogous products has long since been established, certain unfortunate accidents, notably those which recently occurred in St. Louis, Mo., have tended to discredit their use. **The extreme value of the preparations in preventing and curing disease renders it of prime importance, therefore, that action be taken to preserve the confidence of the medical profession and of the community generally in them.**

Selected History of Biologics Regulation

❖ 1902 Biologics Control Act

- ❖ Establishment License, Federal inspection of establishment, dating period, no false labeling**
- ❖ Safety, purity and potency in legislative history and in first regulations**

❖ 1938, 1962 Federal Food, Drug & Cosmetic Act

- ❖ Safety: Ethylene Glycol in Elixir of Sulfonamide**
- ❖ Effectiveness: Thalidomide induced congenital defects**

❖ 1944 PHS Act including Sections 351, 352, 361

- ❖ 351 Safety, Purity, Potency plus FD&CA authorities other than NDA**
- ❖ 352 Allows PHS to prepare biologics for own use, or for public if not available**

❖ 1970 PHS Act Blood and Blood Products

Standards for Biological Products to Assure Continued:

❖ SAFETY

- ❖ **Unsuspected, unknown adventitious agents**
 - ❖ Tetanus, hepatitis viruses, HIV, PERV
- ❖ **Reversion to wild type**
 - ❖ Polio neurovirulence tests, RCR testing
- ❖ **Immunogenicity (unwanted)**
- ❖ **Insertional mutagenesis**

❖ PURITY

- ❖ **Driven by technology: Pyrogenicity tests, Moisture, Protein sequencing, Mass Spectrometry, NMR**

❖ POTENCY

- ❖ **Not always mechanism of action**
- ❖ **Immunogenicity (wanted), Hemagglutinin (flu), Bioassay (antiviral units)**

❖ And of course efficacy

- ❖ **Proven in clinical trials**
- ❖ **Old and new ways**

Biological Products are Constructs From, Not of, Nature

- ❖ **Nature's native complexity is magnified by the creation of these products**
- ❖ **Nature is far beyond “Been there, done that...”**
- ❖ **Imperative for scientific and regulatory rigor**
- ❖ **Search, then Research**
 - ❖ **Predictors of toxicity for biologics not easily established**
 - ❖ **Unknown risks, such as emerging infectious diseases (PERV)**
 - ❖ **Mechanisms of action poorly understood**
 - ❖ **Rapid paradigm shifts**

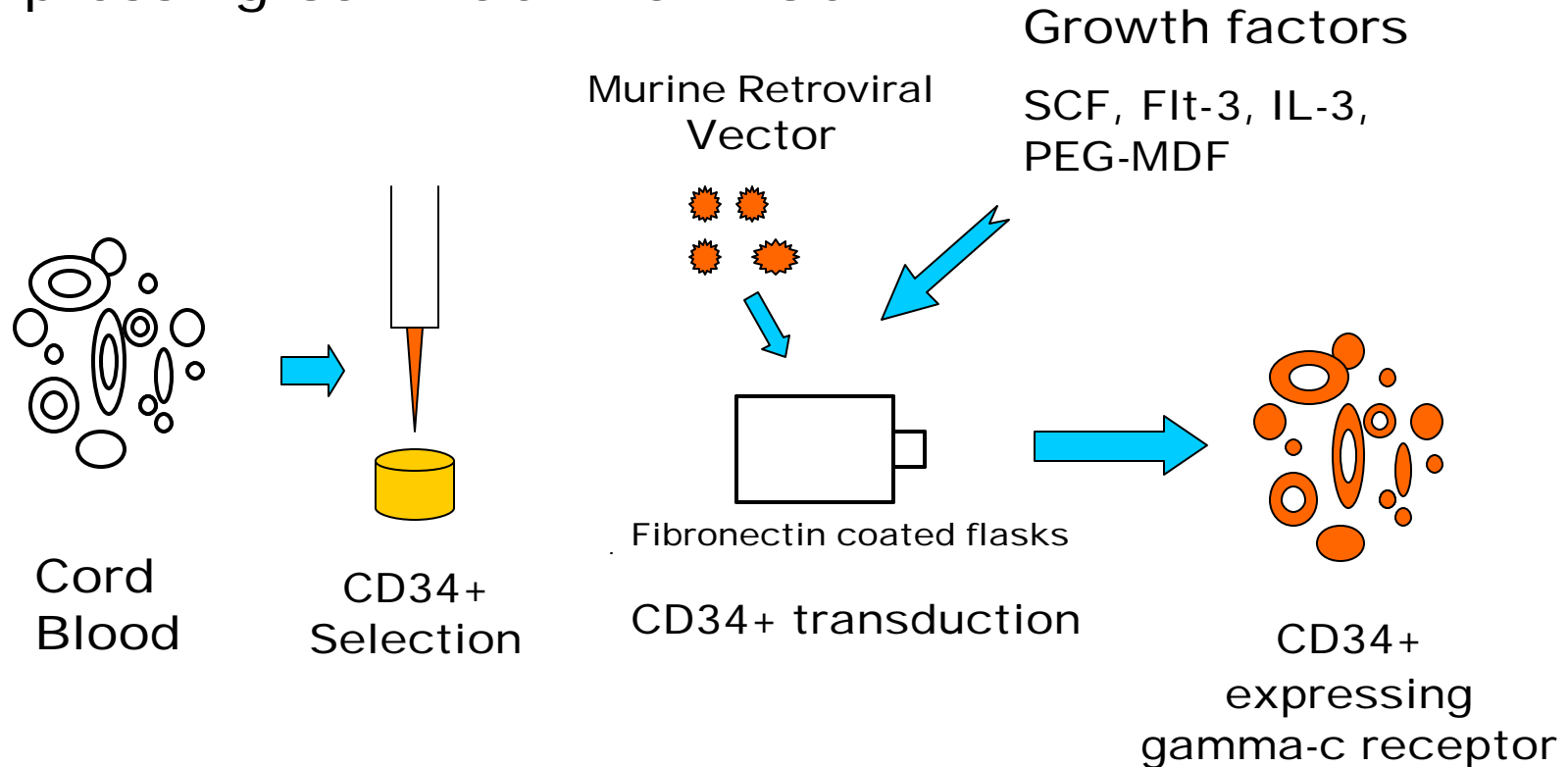
A Lesson From Gene Therapy?

❖ X-linked Severe Combined Immunodeficiency Syndrome (X-SCID)

- ❖ Lack of gamma-c chain with consequent lack of cytokine receptors needed for T-cell function**
- ❖ Death within first year of life from severe recurrent infections**
- ❖ Transplant of HLA-identical marrow >90 % survival; haploidentical transplant 50-70 %**
- ❖ Survivors may still need gamma globulin, unknown long term survival**

Complexity of (a) Gene Therapy Product

Ex Vivo Transduced CD34+ Cells
Expressing GammaC-R for X-SCID



Complexity continued...

❖ Cord Blood

- ❖ Donor screening, adventitious agents, purity, potency

❖ Devices

- ❖ Monoclonal antibodies, surface markers, extracellular matrix

❖ Retroviral Vectors

- ❖ Cell substrates, adventitious agents, reversion to wild type

❖ Specified Products (SCF, Flt-3, etc)

- ❖ Purity, potency, novel use (ancillary, not as primary effector)

❖ Cellular Product

- ❖ Characterization, potency, evidence of gene transduction

Gene Therapy For X-SCID

- ❖ **In France, 9/10 children showed evidence of immune reconstitution following gene therapy**
- ❖ **Late August 2002, one successfully treated child developed leukemia-like symptoms**
- ❖ **FDA Biologics Response Modifier Advisory Committee (BRMAC) reviewed case on 10 October 2002**
- ❖ **Consensus of BRMAC**
 - ❖ **Gene insertion gave both therapeutic effect and caused insertional mutagenesis**
 - ❖ **Because of potential superior immune reconstitution with gene therapy, studies should proceed with caution with stringent testing for clonal expansion of T-lymphocytes**
 - ❖ **Revision of informed consent process for ALL retroviral gene therapies**

Gene Therapy For X-SCID (cont)

- ❖ **Late December 2002, a second successfully treated child developed leukemia-like symptoms In France, with a similar insertion**
- ❖ **FDA Biologics Response Modifier Advisory Committee (BRMAC) reviewed case on 28 Feb 2003**
- ❖ **Consensus of BRMAC**
 - ❖ **Gene insertion at/near LMO-2 site caused insertional mutagenesis leading to leukemias**
 - ❖ **Now cannot be considered a random event**
 - ❖ **GT using HSC for X-SCID should not be primary therapy unless no alternative therapies**

**...learning the lessons of the past
will enable the future:**

***“What can be imagined, will be
done”***

...with hope

...humility

...patience

...compassion