U.S. FOOD & DRUG ADMINISTRATION

Update from the Center for Biologics Evaluation and Research (CBER): Advancing the Development of Complex Biologic Products

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FDLI 2017

Outline

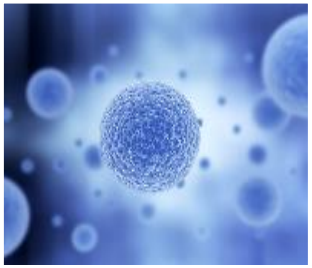
- Products regulated
- Significance of complex biologics
- Product and process
- Relevance of scientific research
- Cutting edge products
- Facilitating development

CBER Regulated Products: Something Old and Something New

Diphtheria Antitoxin

CRISPR/Cas9 Genome Editing

Products Regulated by CBER

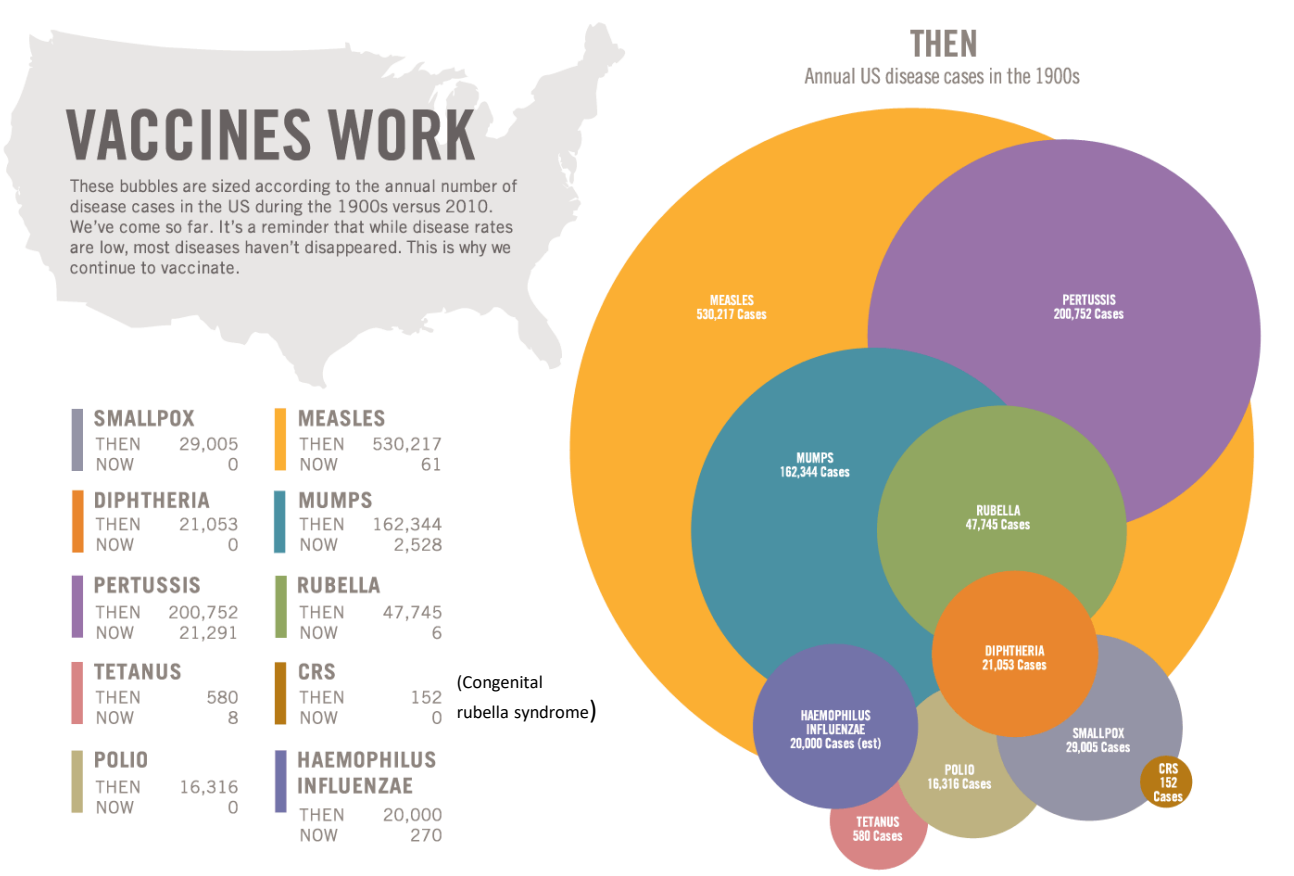


- Blood Products
- Vaccines (preventative and therapeutic)
- Allergenics
- Live Biotherapeutic Products
- Devices Related to Biologics
- Human Tissues and Cellular Products
- Xenotransplantation Products
- Gene Therapies

The Significance of CBER's Complex Biologics

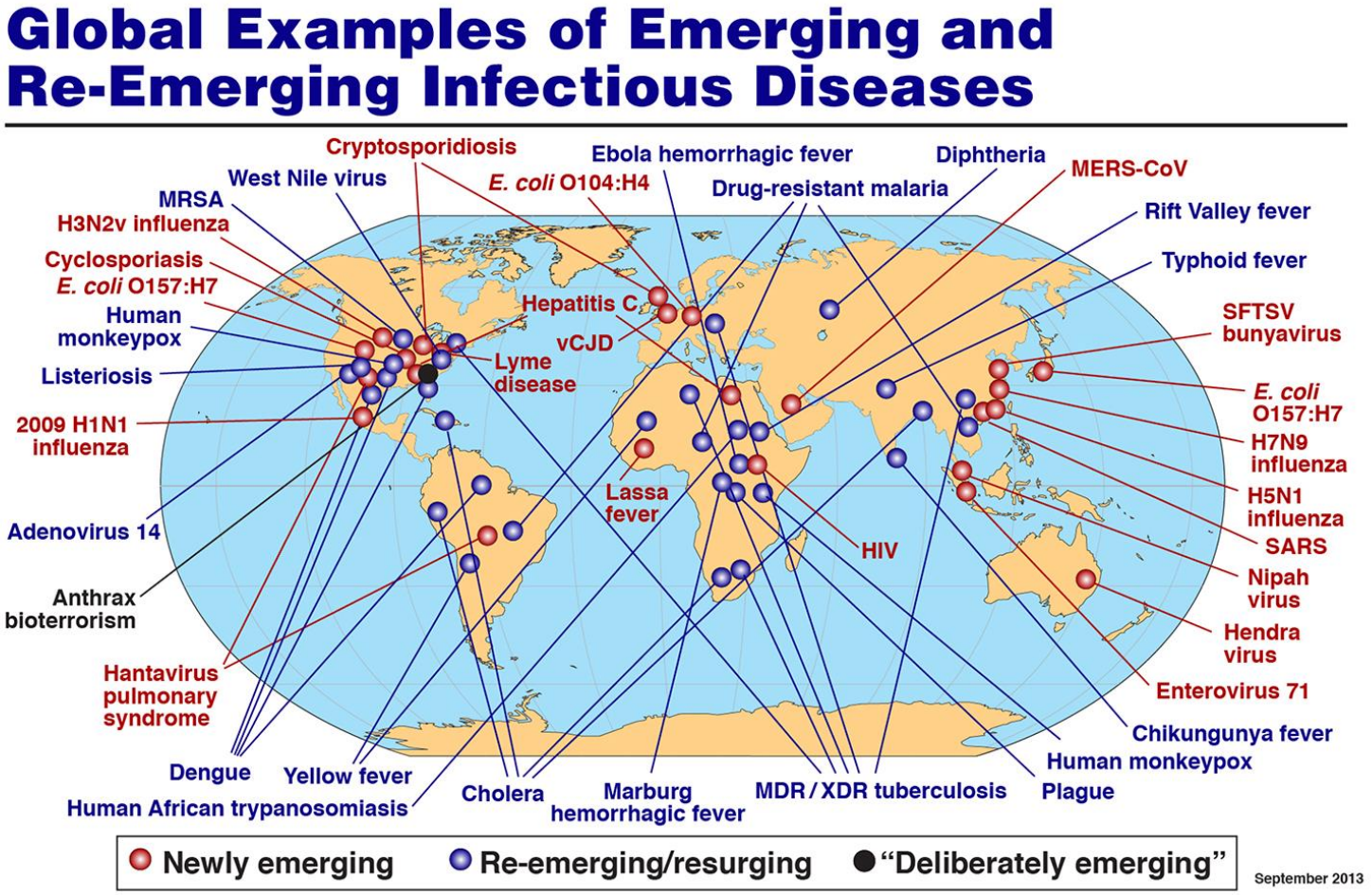
CBER Regulated Products: Vaccines for Disease Prevention

>150 million doses of influenza vaccine given in 2016-2017



[9] Centers for Disease Control and Prevention (CDC). Parents Guide to Childhood Immunizations. http://www.cdc.gov/vaccines/pubs/parents-guide/default.htm. Accessed August 15, 2011.
[10] CDC. Impact of Vaccines in the 20th & 21st Centuries. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/G/impact-of-vaccines.pdf. Updated January 2011. Accessed August 15, 2011.

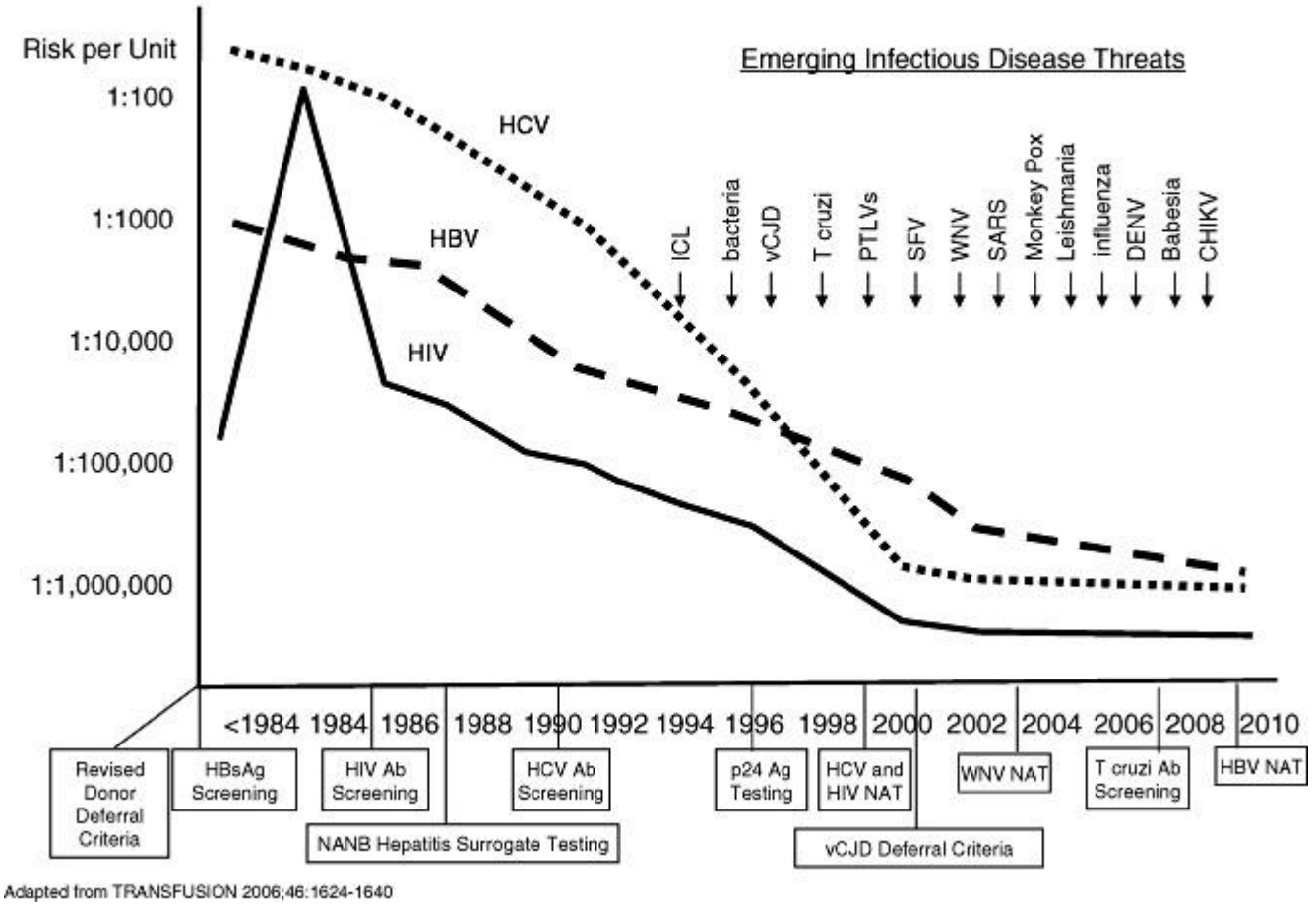
Vaccines are Important for Combating Emerging Infectious Diseases



Source: National Institute for Allergy and Infectious Diseases

CBER Regulated Products: Keeping the Blood Supply Safe

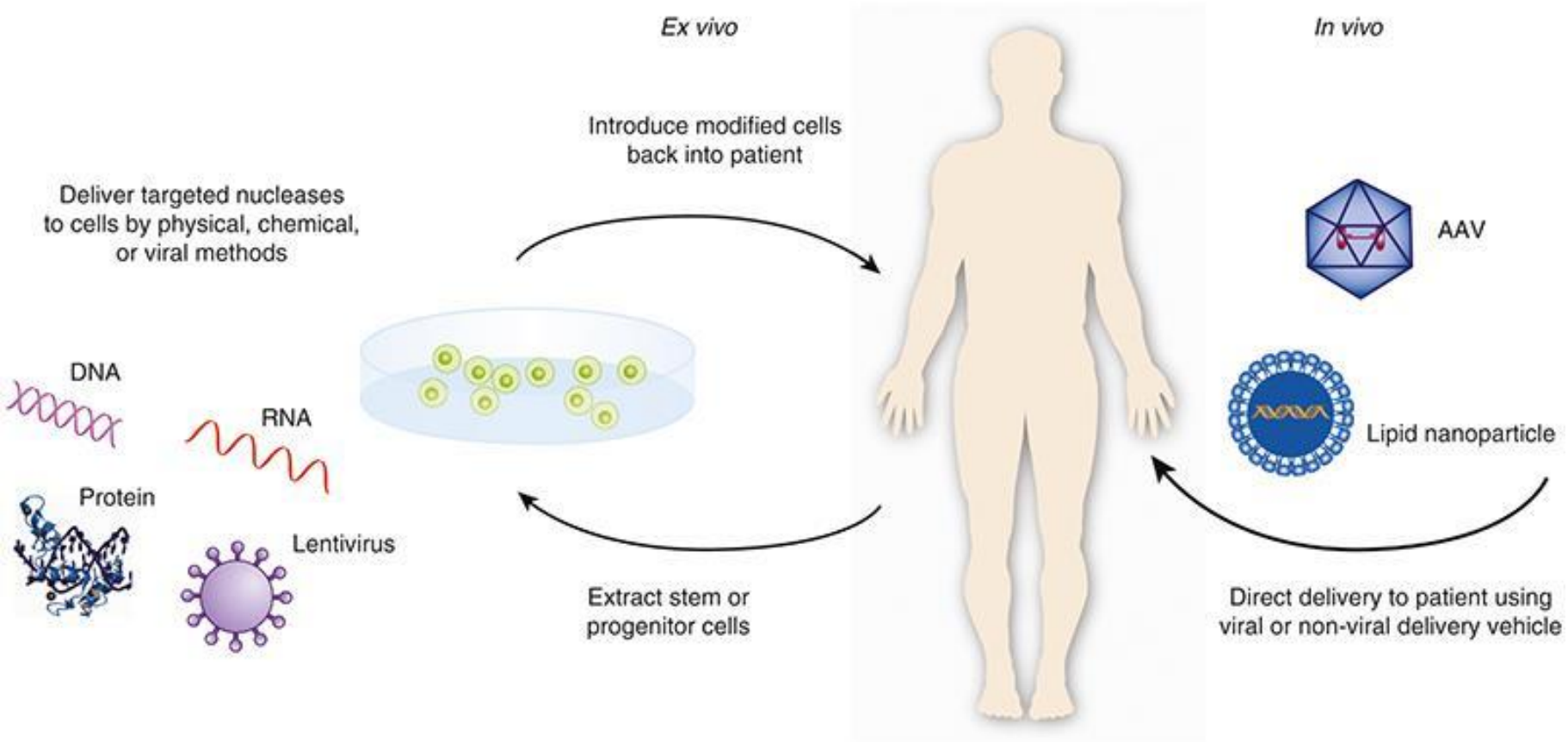
Need for continued vigilance against emerging threats



Adapted from TRANSFUSION 2006;46:1624-1640

CBER Regulated Products: Advanced Therapies at the Leading Edge

Ex vivo or *In vivo* gene therapy to treat various conditions

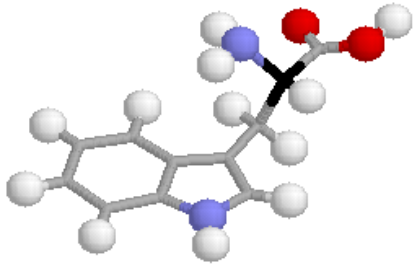


CBER Regulated Products: Regenerative Medicine

- Involves cutting edge science in fields including
  - Cell therapies
  - Therapeutic tissue engineering products
  - Human cell and tissue products
  - Some combination products
- Field with great promise that goes directly to the FDA's role in helping meet unmet medical need

Complex Biologics:
Product and Process Intertwined

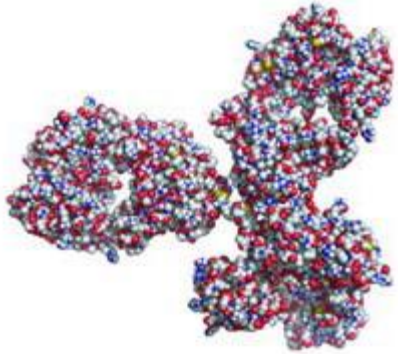
Complexity of Therapeutics



One subunit of a protein

10^2 Atoms

L-tryptophan
Small Molecule Drug



Protein composed of about 1100 subunits

10^5 Atoms

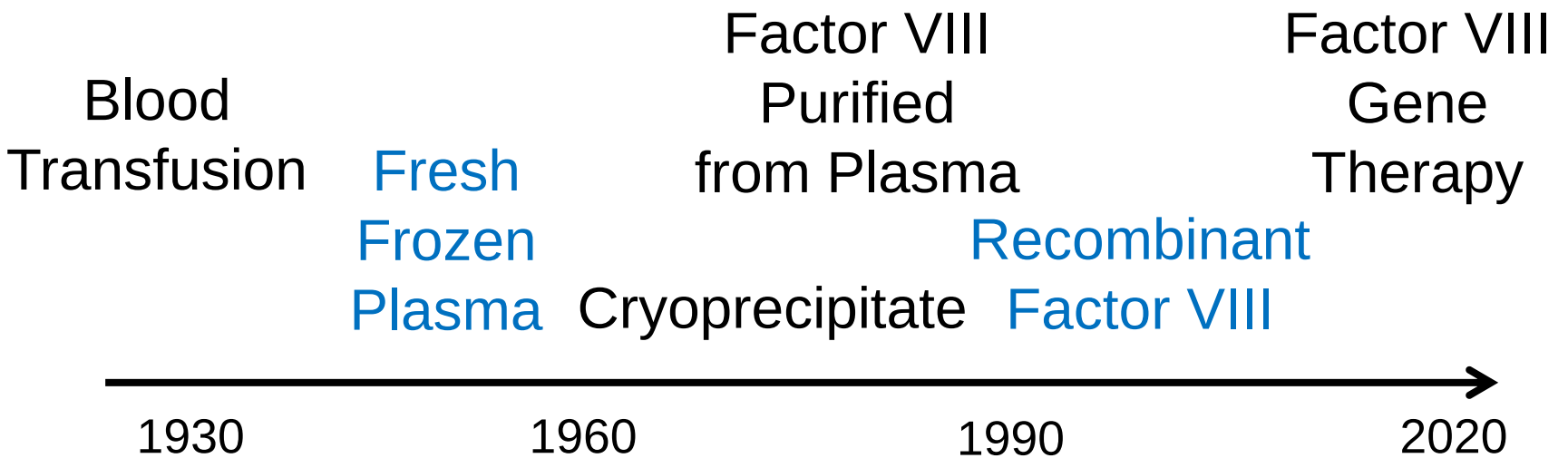
IgG antibody molecule
Protein Biologic

Cell composed of about 3.6×10^6 proteins

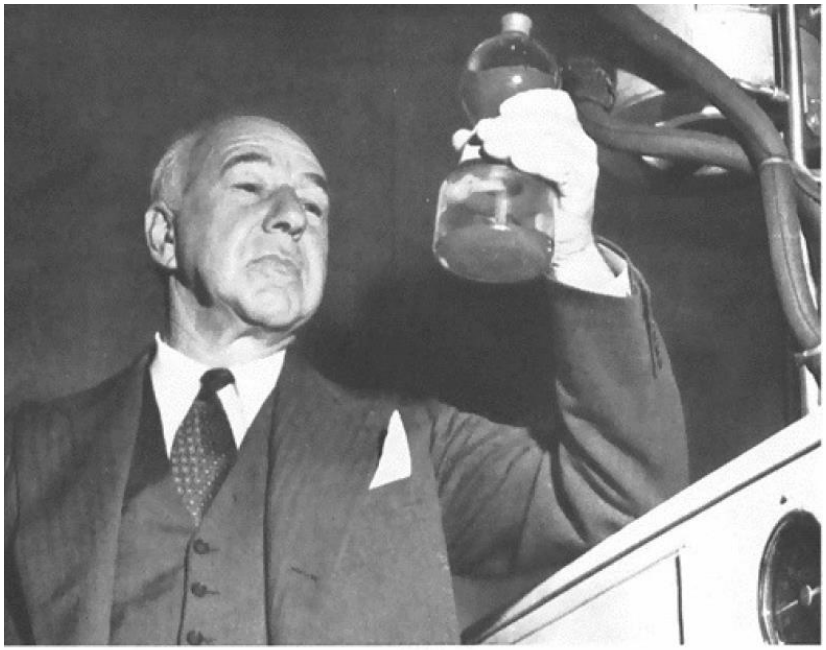
10^{14} Atoms

Mesenchymal stem cell
Cellular Biologic

Evolution of Hemophilia A Treatment

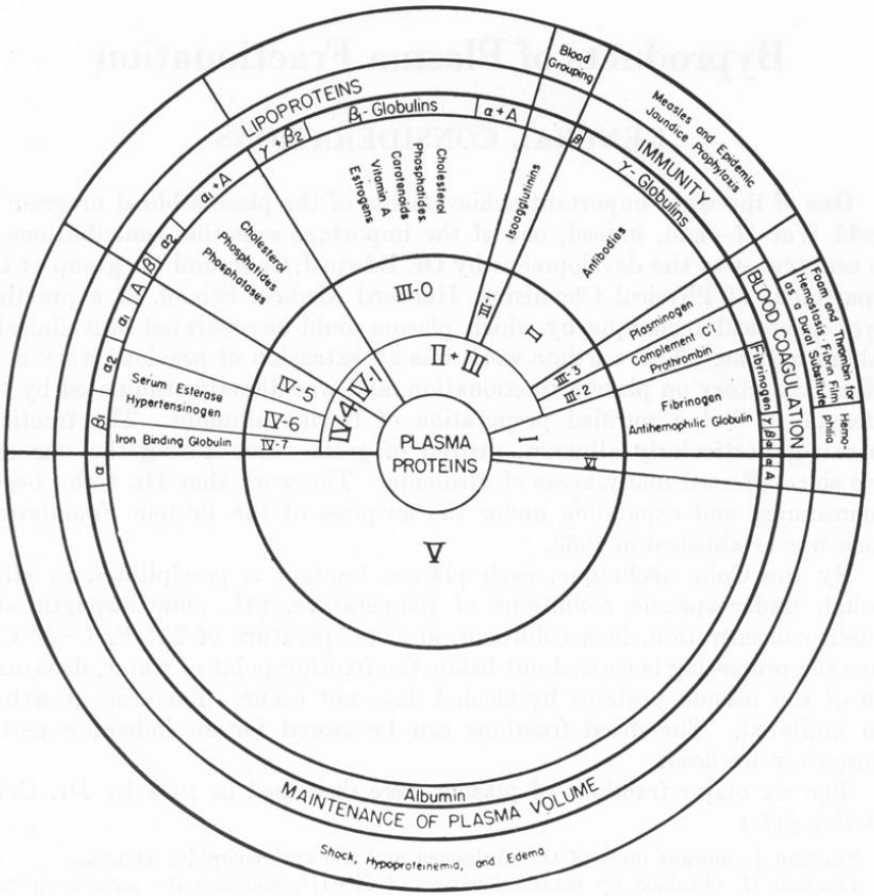


Plasma Derivative Preparation



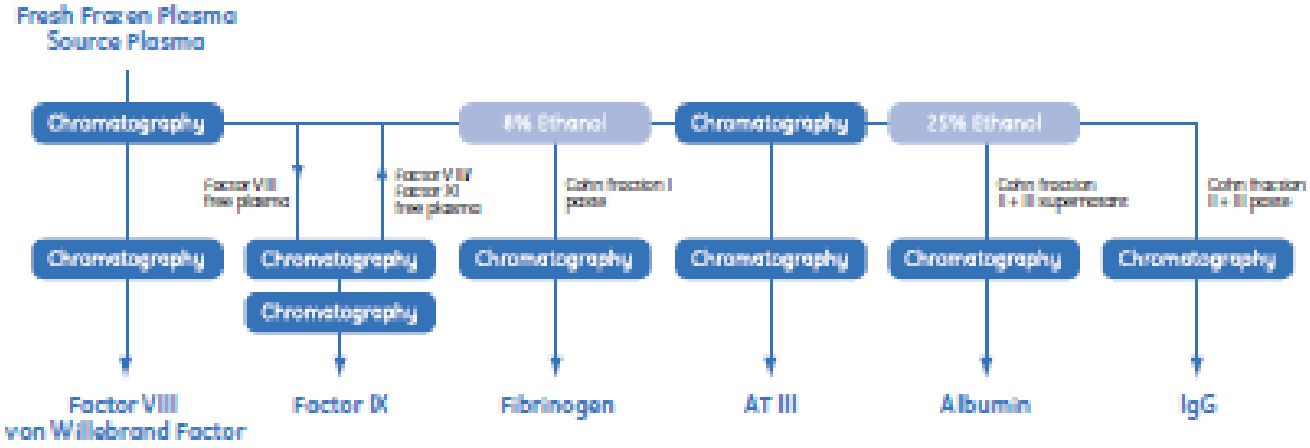
Edwin J. Cohn

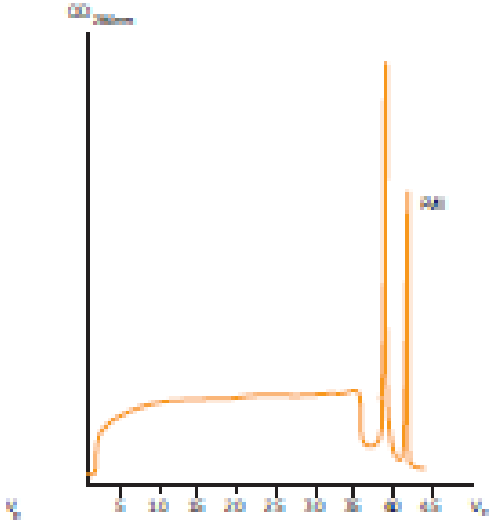
CHART 7.—*Fractional distribution of various components of plasma, proportion separated in each fraction, and uses for each to 1947*



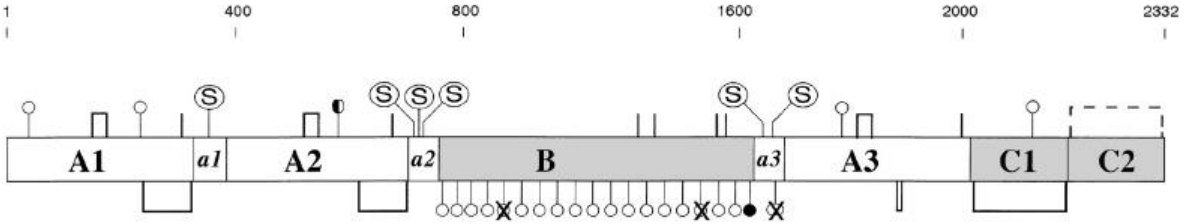
Source: Cohn, E. J.: The Separation of Blood into Fractions of Therapeutic Value. Ann. Int. Med. 26: 341-352, March 1947.

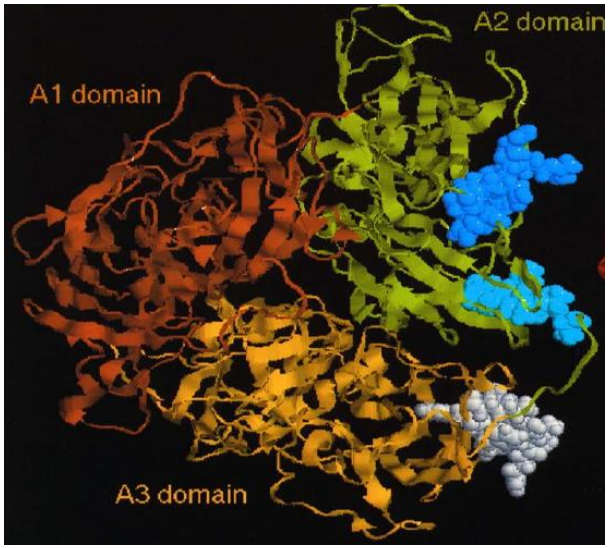
Factor VIII Purification from Plasma





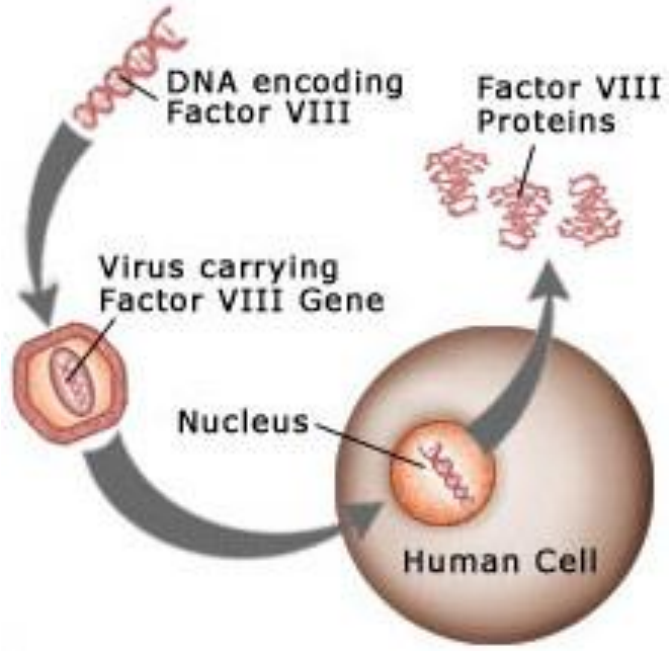
Recombinant Factor VIII





From: Lenting PJ, van Mourik JA, and Mertens K. Blood 1998; 92:3983-3996.

Gene Therapy for Hemophilia A

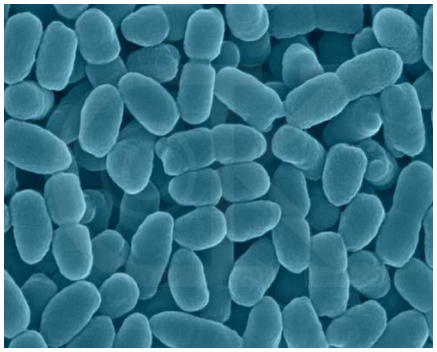


Vector	Capacity (kb)	Immune Response	Vector Genomes	Advantages	Problems
Retrovirus	8	Low	Integrated	Stable expression in daughter cells	Works only in dividing cells; oncogenesis
Lentivirus	8	Low	Integrated	Stable expression in daughter cells	Integration may cause oncogenesis
Adenovirus	8	High	Episomal	Efficient transductio n of most tissues	Capsid causes strong immune response
Helper-dependent adenovirus	30	High	Episomal	Efficient transductio n of most tissues	Capsid causes strong immune response
Adeno-associated virus	≈5	Low	Episomal (>90%) Integrated (<10%)	Non-pathogenic	Small capacity; immune response

From:George LA, Fogarty PF. Semin Hematol 2016; 53:46-54.

Complex Biologics: Relevance of Applied Scientific Research

Example of Vaccine Research



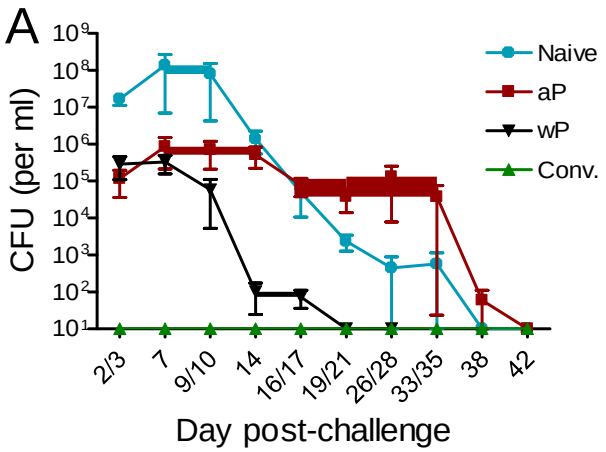
- Recently there has been a resurgence in whooping cough caused by *B. pertussis*

- CBER scientists developed a non-human primate model for this disease that could facilitate further vaccine development
  - Warfel JM et al. Infect Immun. 2012; 80: 1530–1536.

Baboon Model Suggests Mechanism of Vaccine Failure

- Acellular pertussis vaccine (current) compared to whole cell pertussis vaccine (older generation)
- Both vaccines induced robust antibody responses, but T cell responses were significantly different

Acellular vaccine protected against disease related to pertussis, but failed to prevent infection and transmission

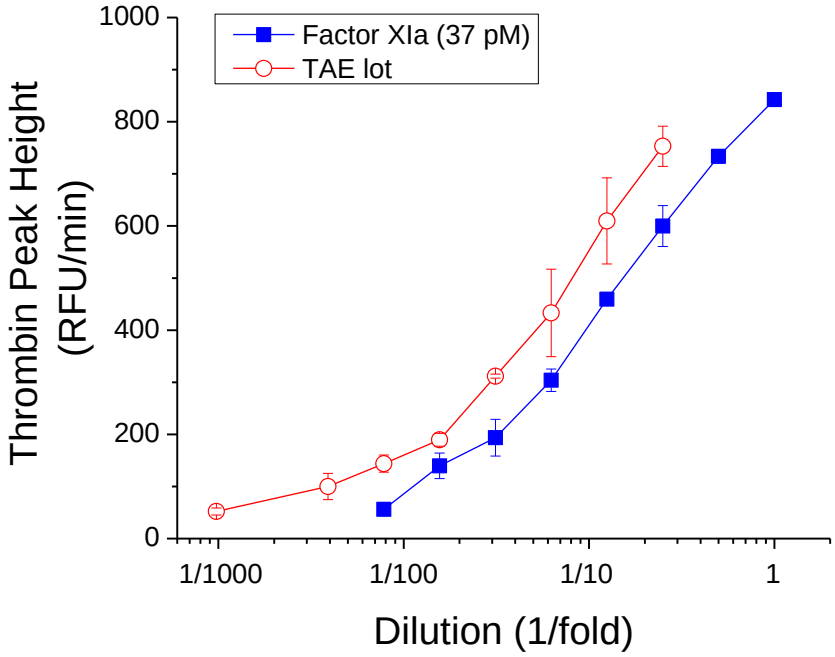


Example of Blood Research

- Use of immune globulin products associated with a number of thrombotic serious adverse events that were reported to FDA
- Included myocardial infarction, stroke, and venous thromboembolism
- Causes of adverse events were uncertain
- During a cluster of cases associated with specific lots of immune globulins researchers examined factor XIa levels, a potential risk factor

Identifying and Addressing a Cause of Thrombotic Events

Similar results were obtained when FXIa was spiked into five different IGIV products



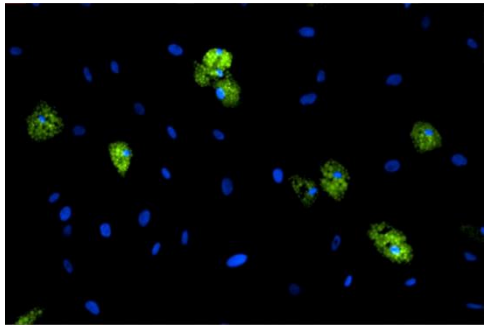
- Assay transfers: on-site training and consultations with industry and regulators
- 1st international reference reagent for Activated Blood Coagulation Factor XI (FXIa), Human, NIBSC 11/236

Menis M et al. Am J Hematol. 2013; 88:1035-40.

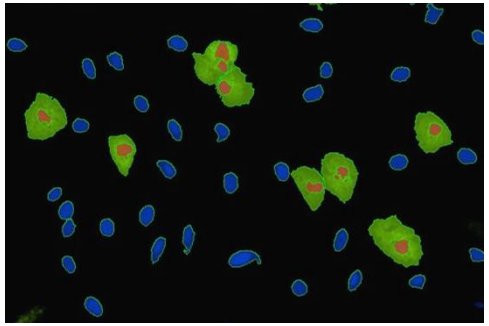
Example of Cell, Tissue and Gene Therapy Research

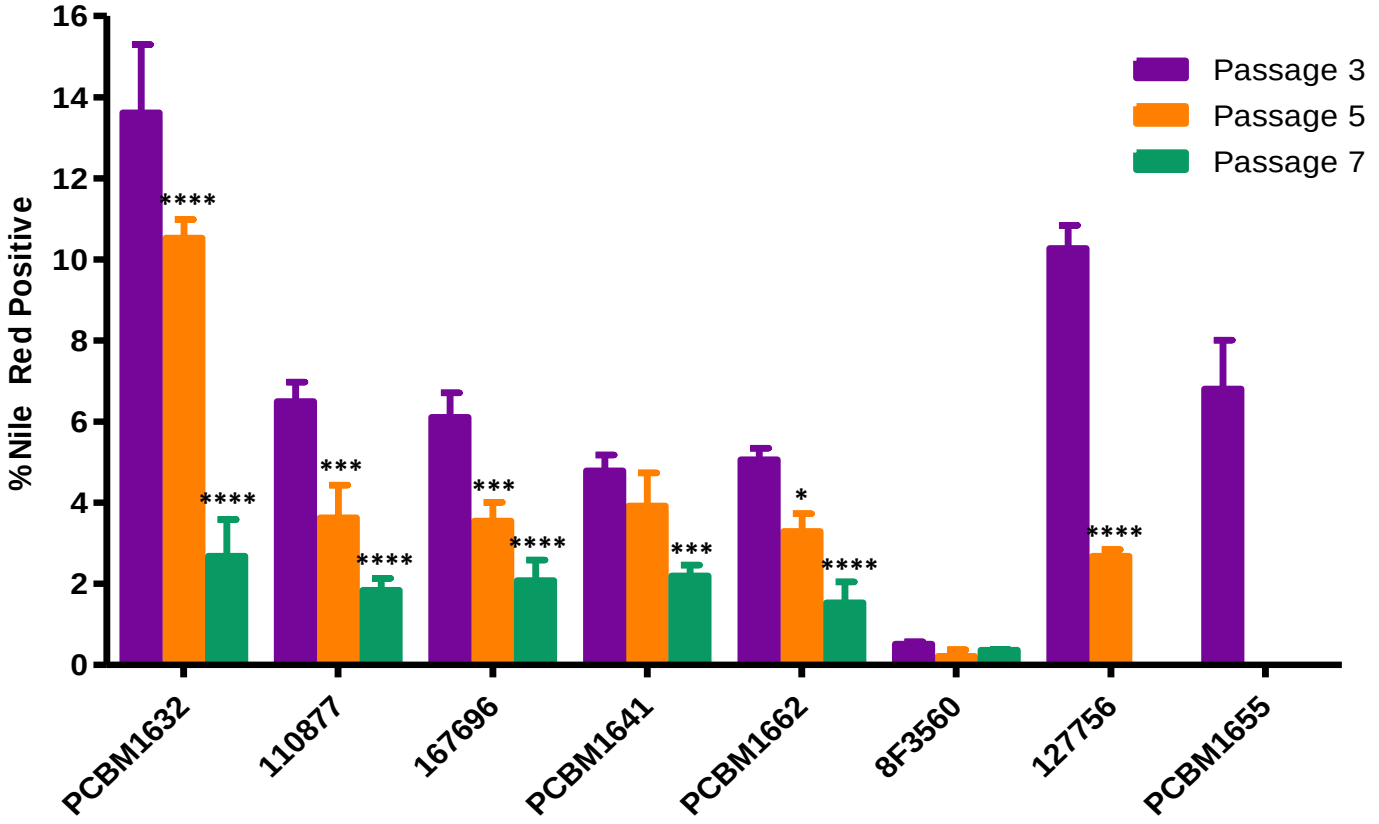
- How best to characterize cellular therapies is still evolving
  - Particularly the case for stem cells taken from an individual
- The parameters that define how cells that are administered to an individual will ultimately perform in terms of safety and efficacy are not yet well-defined
- A multidisciplinary approach of applied science using molecular genetics and cell biology may help elucidate such parameters

Ability of Cells to Differentiate Depends on Cell Line and Passage



Automated microscopy-based quantification





Lo Surdo JL et al. Cytotherapy. 2013; 15:1527-40.

Example of Biostatistics and Epidemiology Research

- Use of real world evidence at FDA for evaluation of product safety has been ongoing for a number of years using large healthcare databases
  - Sentinel, Medicare, Healthcore, others
- Rigorous methodology developed including protocol development and execution to facilitate signal identification and confirmation
- Investigation of the ability of real world evidence to evaluate effectiveness is in progress

Comparison of High-Dose and Standard-Dose Influenza Vaccine

- Used Medicare Database to evaluate efficacy of high-dose (929,730 recipients) versus standard-dose vaccine (1,615,545 recipients)
- High-dose vaccine was 22% (95% CI 15-29) more effective than the standard-dose vaccine for prevention of probable influenza infections and 22% (95% CI 16-27%) more effective for prevention of influenza hospital admissions
- In agreement with a randomized clinical trial conducted in 31,989 individuals which showed relative efficacy of 24.2% (95% CI 9.7-36.5)

Izurieta H et al. Lancet 2015; 15:293-300.

Regulatory Science at FDA

- Fills an important niche to meet our regulatory mission and facilitate product development through availability of scientific experts who
  - Understand the regulatory process
  - Proactively address regulatory science gaps
  - Respond to public health emergencies

Complex Biologics: Products at the Cutting Edge of Science and Medicine

Chimeric Antigen Receptor-T Cells

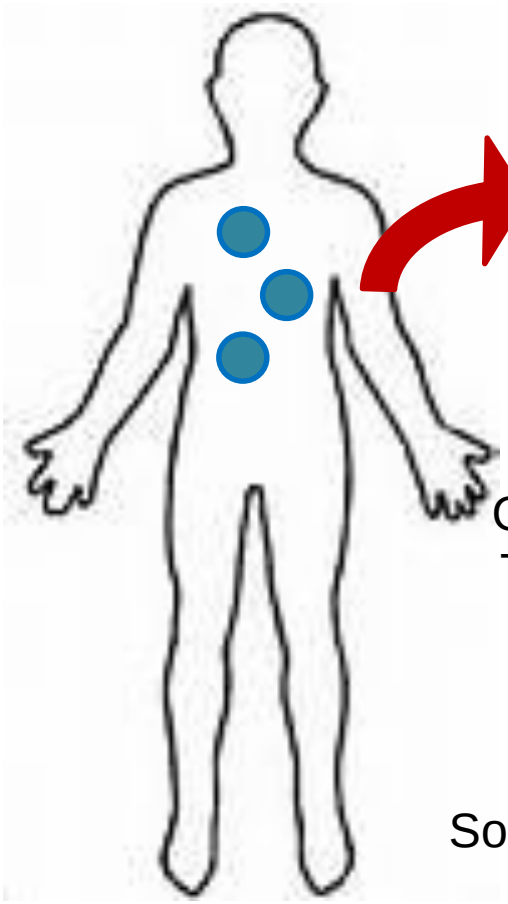
Chimeric Antigen Receptor-T Cells

- Chimeric antigen receptor-T cells (CAR-T cells) represent a cell-based gene therapy with potential applications to multiple diseases
  - Hematologic malignancies
  - Solid tumors
  - Infectious disease
  - Autoimmune disease
- Possibility to provide therapeutic benefit with an extended duration of effect

Chimeric Antigen Receptor-T Cells

- Conventional *ex vivo* expanded T cells targeting tumor antigens show some efficacy, but poor persistence
- Genetically modified T cells harness immunity (cytotoxic functions, cytokine secretion, etc.) to attack tumor or other immune effector cells
- Gene transfer improves functional properties of transduced T cells (e.g., antigen recognition, effector function)

Basic Overview of CAR-T Therapy



Patient

Apheresis Product

T cell activation and transduction with gene transfer vector

Expand in culture CD3/CD28 beads ± IL-2 / IL-15

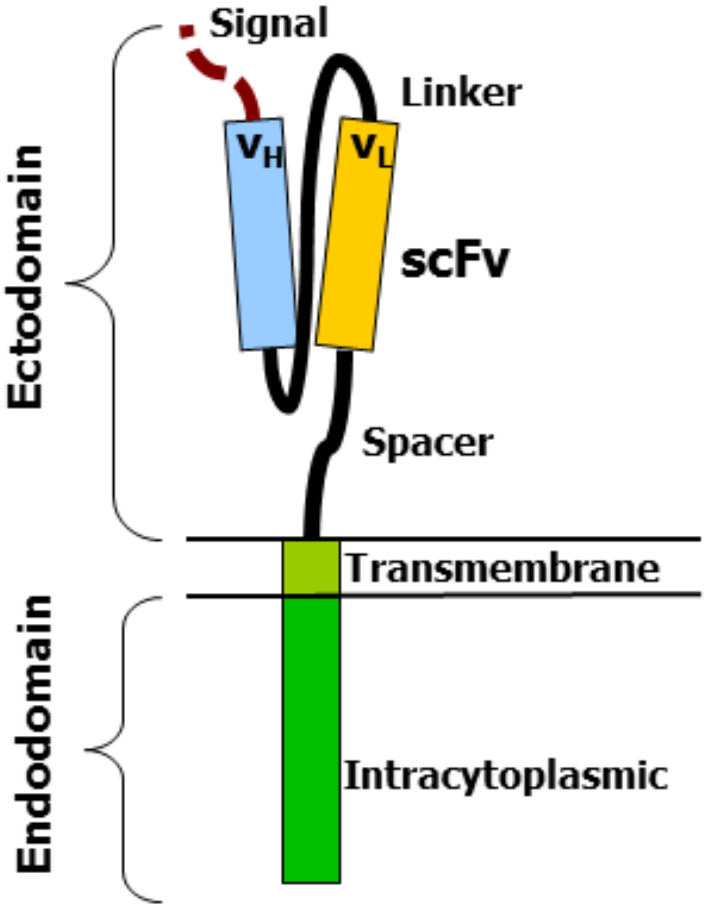
Dose formulation Product testing

Gene modified T cell Infusion

Patient may receive pre-conditioning chemotherapy prior to infusion
Sometimes cytokine support (IL-2) post infusion

Genetic Modification: Introduction of Chimeric Antigen Receptor

- Using molecular genetics, novel protein receptors can be created that combine features of different proteins into one
- This allows one to both target and activate T cells to eliminate a cancerous or undesirable cell type



Potential Advantages to Use of Genetically-Modified Cellular Therapies

- Appropriate methods can be used to address the issue of location of genomic integration
  - Use of genome editing possible (CRISPR/Cas9*)
- Ability to select appropriately transduced cells for administration to recipients
  - Use of next generation sequencing
- It is possible to turn off the effect of the cells, if necessary, through use of certain approaches
  - Use of suicide genes

*Clustered regularly interspaced short palindromic repeats/Cas9 enzyme gene editing system

Potential Challenges to Use of Genetically-Modified Cellular Therapies

- Process must be developed to consistently manufacture and characterize cells
- Logistics facilitating production and delivery of cells must be carefully orchestrated
- Administration of therapies may be associated with various short and longer term side effects
  - Acute inflammatory process
    - Cytokine release syndrome
  - Immune function

Complex Biologics: Facilitating Development

Expedited Pathways

- Fast Track Designation
- Breakthrough Designation (2012 – FDASIA)
- Accelerated Approval
- Priority Review

2016 – 21st Century Cures Act

- Patient-focused drug development
- Advancing New Drug Therapies
- Modern Trial Design and Evidence Development
- Patient Access to Therapies and Information
- Antimicrobial Innovation and Stewardship
- Medical Device Innovations
- Improving Scientific Expertise and Outreach at FDA
- **Regenerative Medicine Provisions**

Regenerative Medicine Advanced Therapy (RMAT) Provisions

- Section 3033
  - Accelerated Approval for Regenerative Advanced Therapies
- Section 3034
  - Guidance Regarding Devices Used in the Recovery, Isolation, or Delivery of Regenerative Advanced Therapies
- Section 3035
  - Report on Regenerative Advanced Therapies
- Section 3036
  - Standards for Regenerative Medicine and Regenerative Advanced Therapies

RMAT Designation (Section 3033)

- A designation has been created to expedite the development and review of regenerative advanced therapies
- Applies to certain cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products
  - May include genetically modified cells
- Products must be intended for serious or life-threatening diseases or conditions

RMAT Designation (Section 3033)

- Preliminary clinical evidence must indicate potential to address unmet medical needs
- Designation requests to FDA from sponsors must receive a response within 60 days
- Designated products are eligible as appropriate for priority review and accelerated approval

RMAT Designation (Section 3033)

- Post-approval requirements for accelerated approval can be fulfilled as appropriate through submission of
  - Clinical evidence, clinical studies, patient registries or other sources of real world evidence such as electronic health records
  - The collection of larger confirmatory datasets as agreed upon
  - Post-approval monitoring of all patients treated with such therapy prior to approval of the therapy

Process for Regenerative Medicine Advanced Therapy Designation

- Sponsor can request with a new investigational new drug submission or as an amendment to an existing one
- Request for designation should describe
  - How definition of regenerative medicine therapy is met
  - How criterion to address a serious or life-threatening disease or condition is met, and
  - Preliminary clinical evidence indicating that the drug has the potential to address an unmet medical need

Website with information about process: http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm

Progress on RMAT Designation

- Already receiving RMAT designation requests
- Though FDA generally cannot comment on unapproved applications, able to note that one company has issued a press release noting that they have received RMAT designation
- We look forward to continuing to work with sponsors of these products and other stakeholders to help make these exciting new therapies available to those in need.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