

BACK TO THE FUTURE: A RECENT HISTORY OF HEMOPHILIA TREATMENT

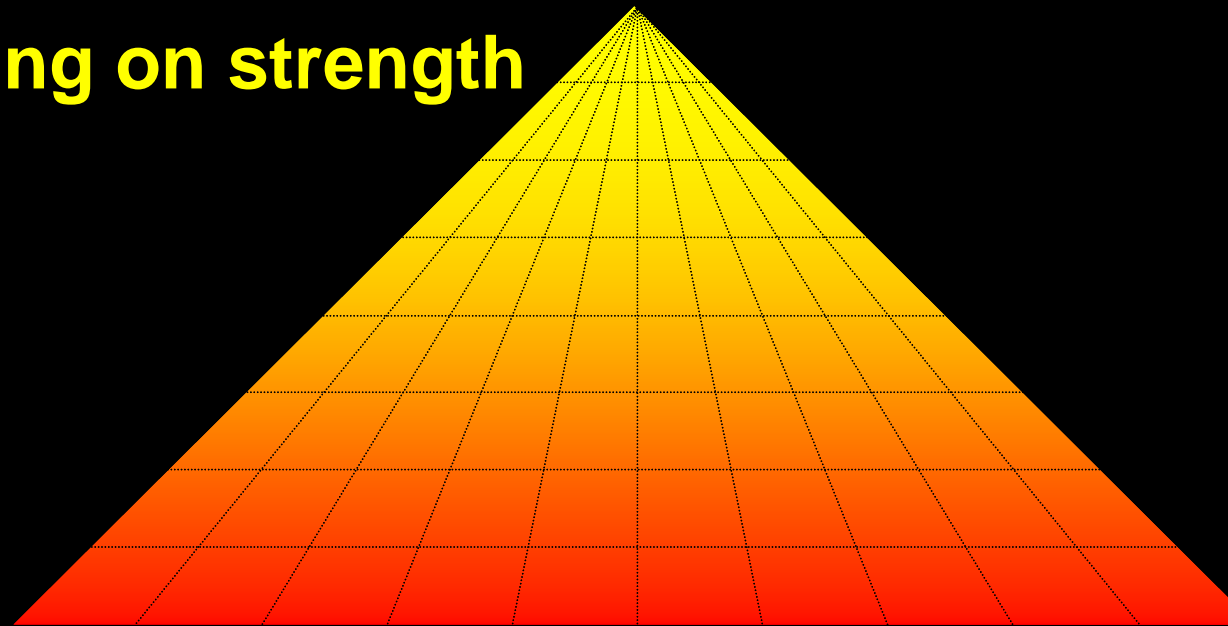
Pier M. Mannucci

**Angelo Bianchi Bonomi Hemophilia and
Thrombosis Centre**

**Department of Medicine and Medical Specialties
University of Milan, Italy**

COMPARTMENTALIZATION OF MY TALK

- **The 1970s: the success story of the decade**
- **The 1980s: many shadows, a few lights**
- **After the 1990s: a new golden era**
- **What is next: building on strength**



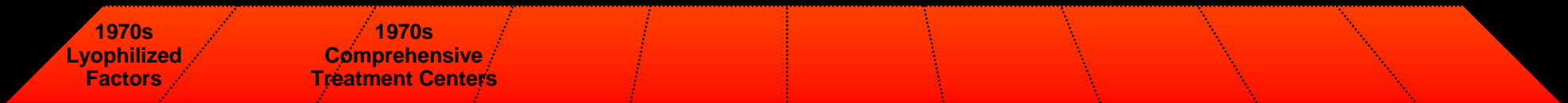
A white starburst shape with a red outline, containing the text "1970s Lyophilized Factors".

**1970s
Lyophilized
Factors**

A red trapezoidal bar with a gradient from light red to dark red, divided into several segments by vertical dashed lines.

**1970s
Lyophilized
Factors**

The 1970s: the success story of the decade



The 1970s: the success story of the decade



**1970s
Home
Treatment**



**1970s
Lyophilized
Factors**

**1970s
Comprehensive
Treatment Centers**

**1970s
Home
Treatment**

The 1970s: the success story of the decade

A white starburst graphic with a red outline, containing the text "1970s Prophylaxis Programs".

**1970s
Prophylaxis
Programs**

**1970s
Lyophilized
Factors**

**1970s
Comprehensive
Treatment Centers**

**1970s
Home
Treatment**

**1970s
Prophylaxis
Programs**

The 1970s: the success story of the decade

A white starburst graphic with a red outline, containing the text '1970s Desmopressin (DDAVP)'.

**1970s
Desmopressin
(DDAVP)**

**1970s
Lyophilized
Factors**

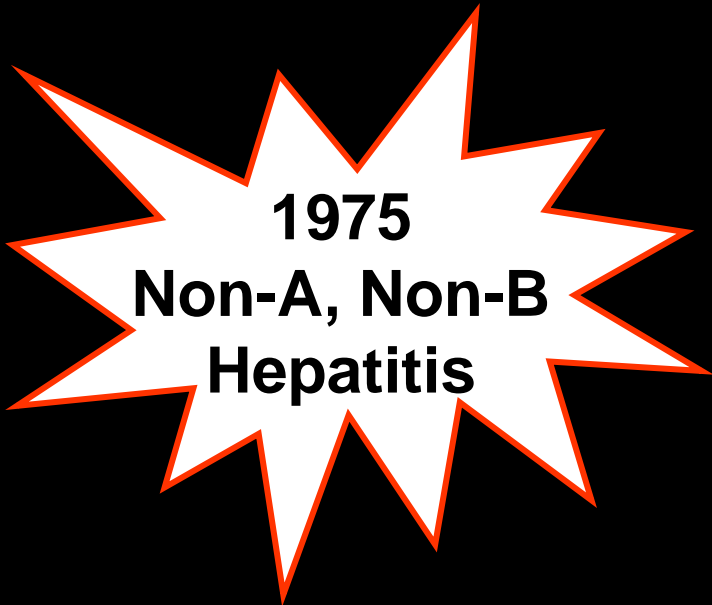
**1970s
Comprehensive
Treatment Centers**

**1970s
Home
Treatment**

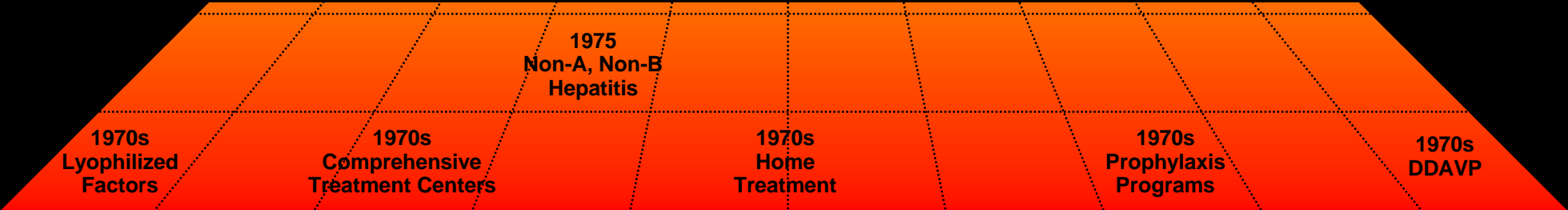
**1970s
Prophylaxis
Programs**

**1970s
DDAVP**

The 1970s: the success story of the decade



**1975
Non-A, Non-B
Hepatitis**



**1975
Non-A, Non-B
Hepatitis**

**1970s
Lyophilized
Factors**

**1970s
Comprehensive
Treatment Centers**

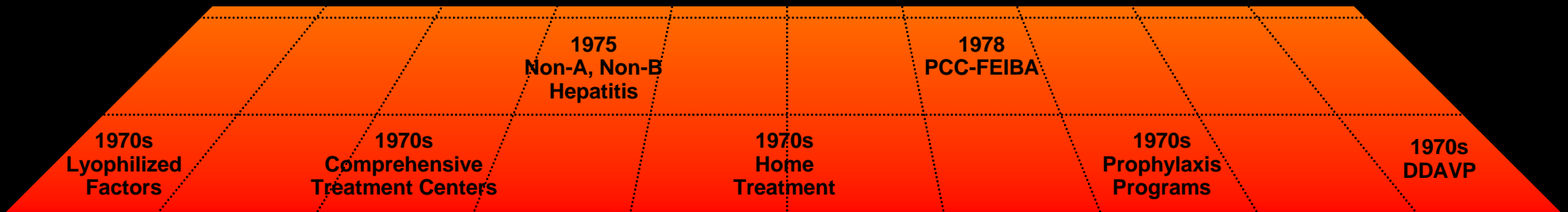
**1970s
Home
Treatment**

**1970s
Prophylaxis
Programs**

**1970s
DDAVP**

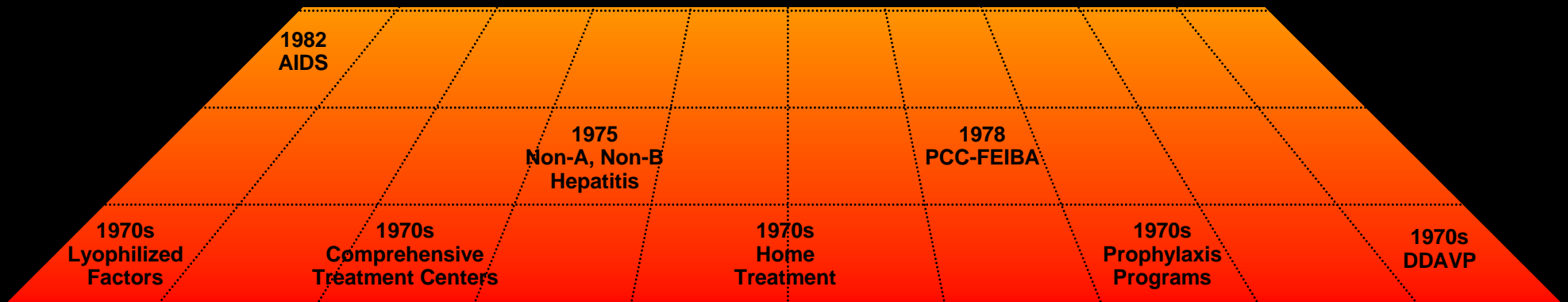
The 1970s: the success story of the decade

**1978
PCC- Feiba**



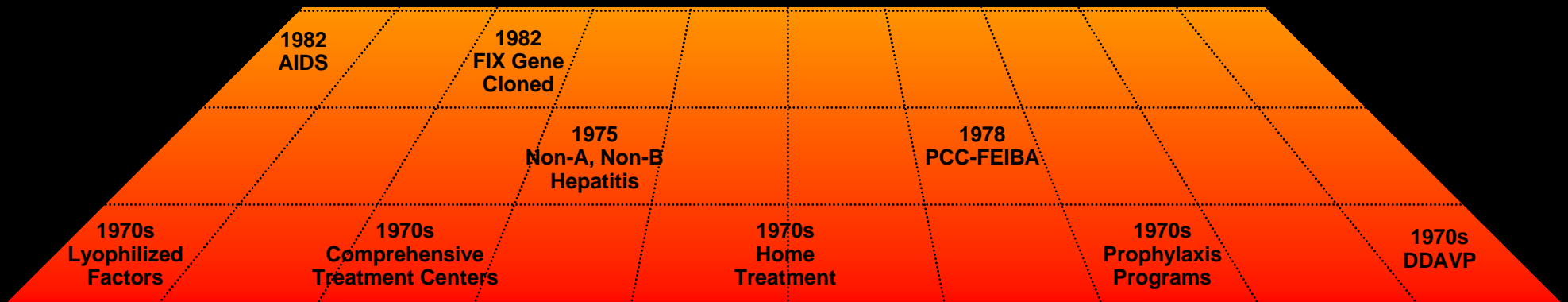
The 1970s: the success story of the decade

**1982
AIDS**



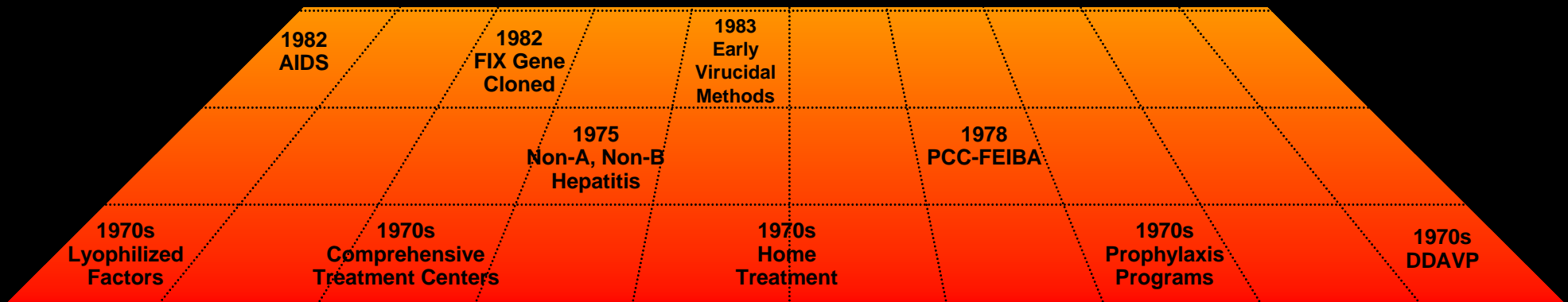
The 1970s: the success story of the decade

**1982
FIX Gene
Cloned**



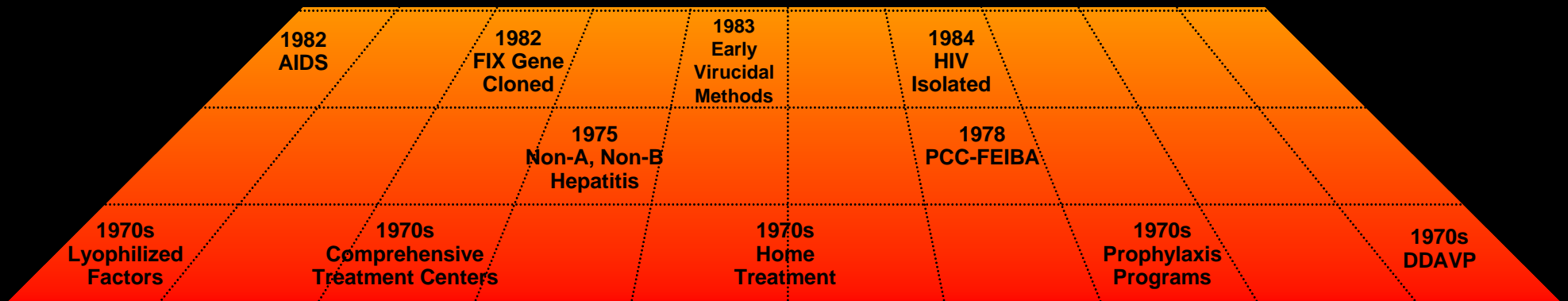
The 1970s: the success story of the decade

**1983
Early Virucidal
Methods
(Dry-Heating)**



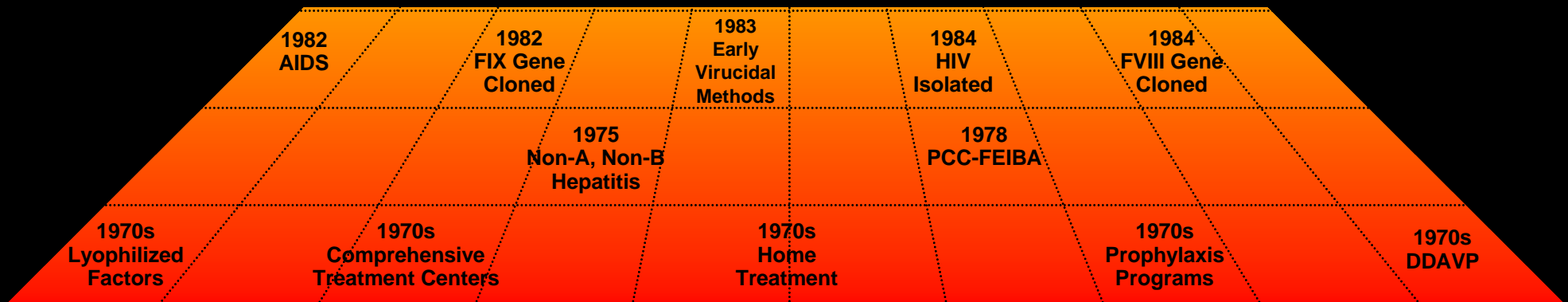
The 1970s: the success story of the decade

**1984
HIV
Isolated**



The 1970s: the success story of the decade

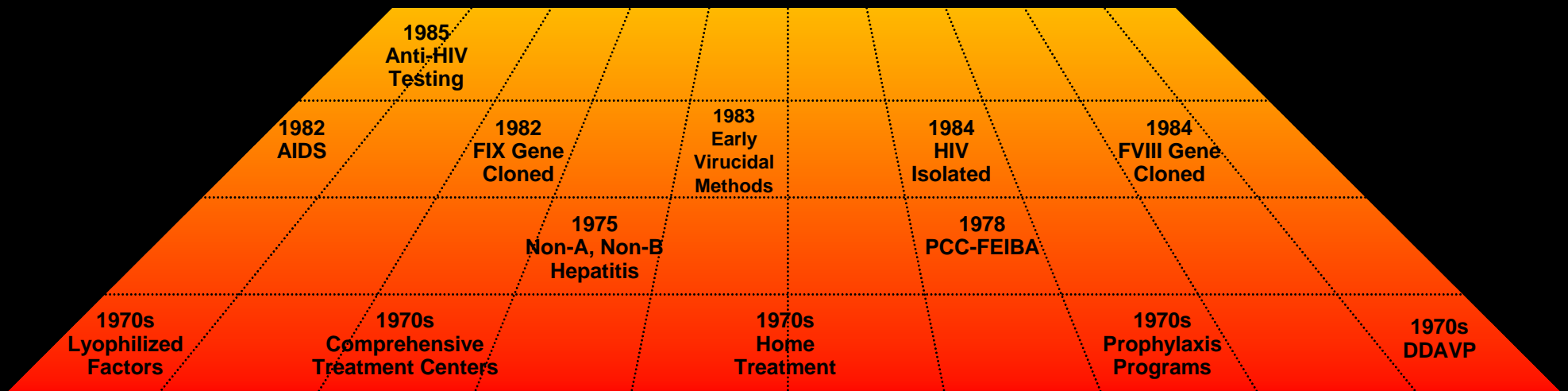
**1984
FVIII Gene
Cloned**



The 1970s: the success story of the decade

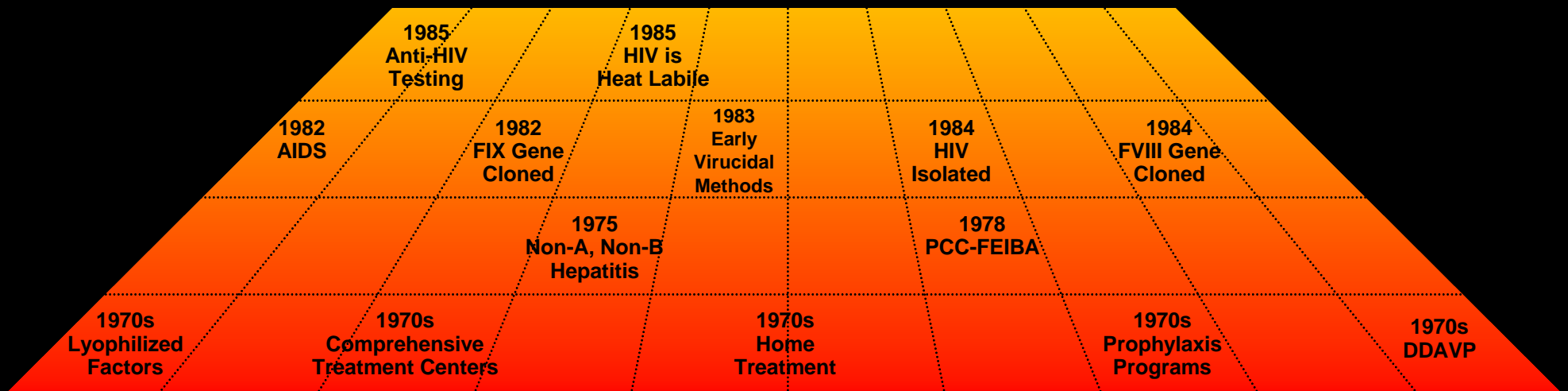


**1985
Anti-HIV
Testing**



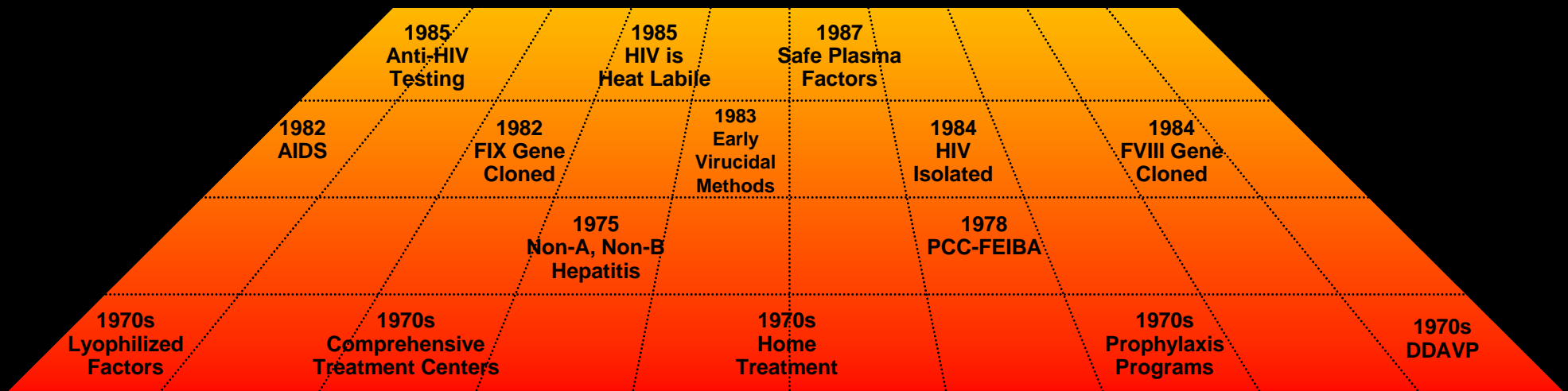
The 1970s: the success story of the decade

**1985
HIV is
Heat Labile**

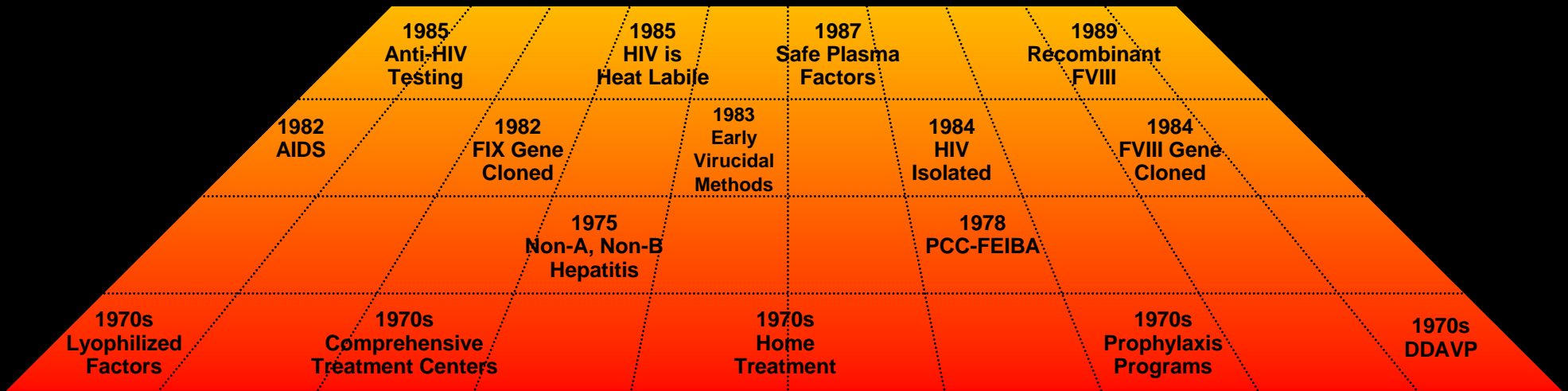


The 1970s: the success story of the decade

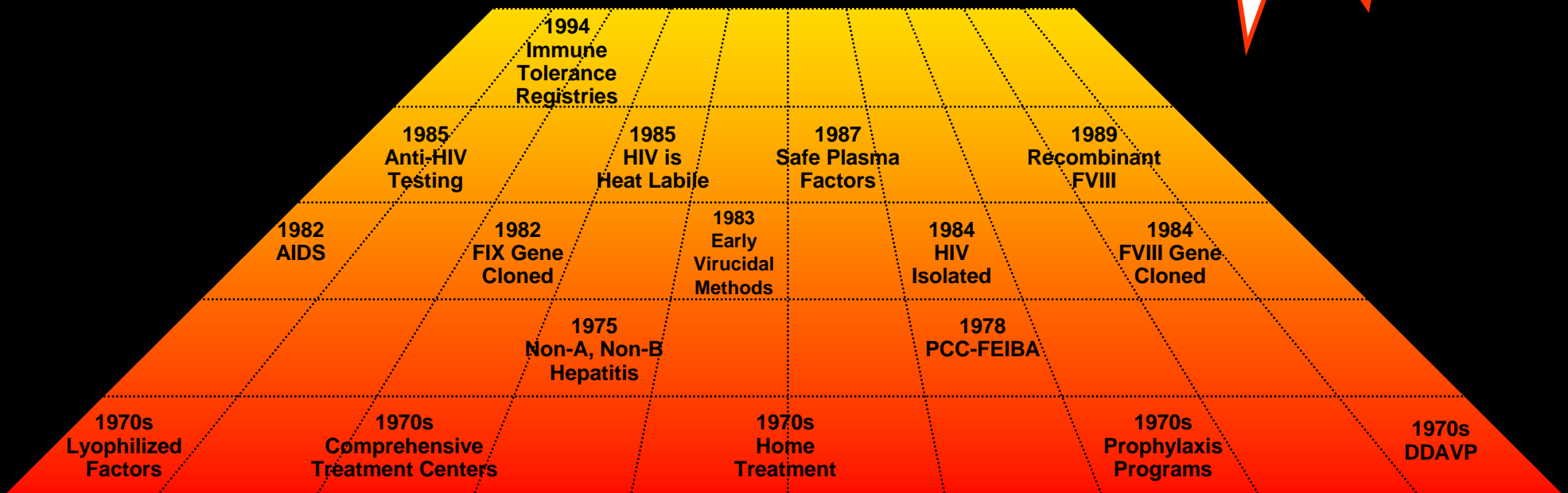
1987 Safe Plasma Factors



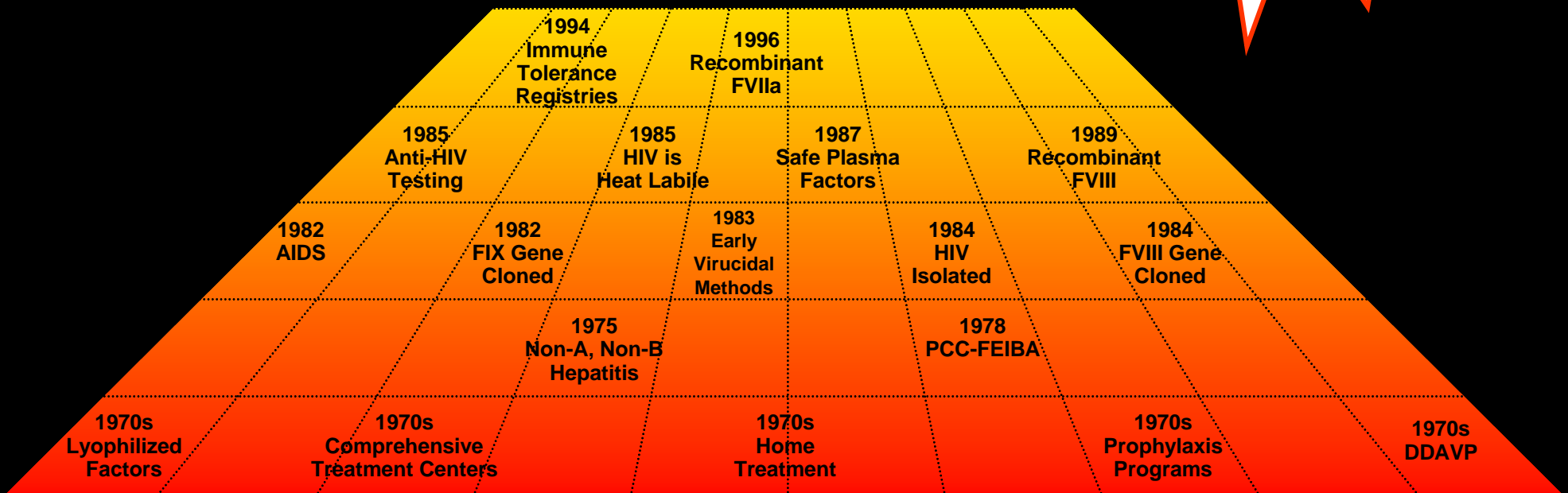
The 1970s: the success story of the decade



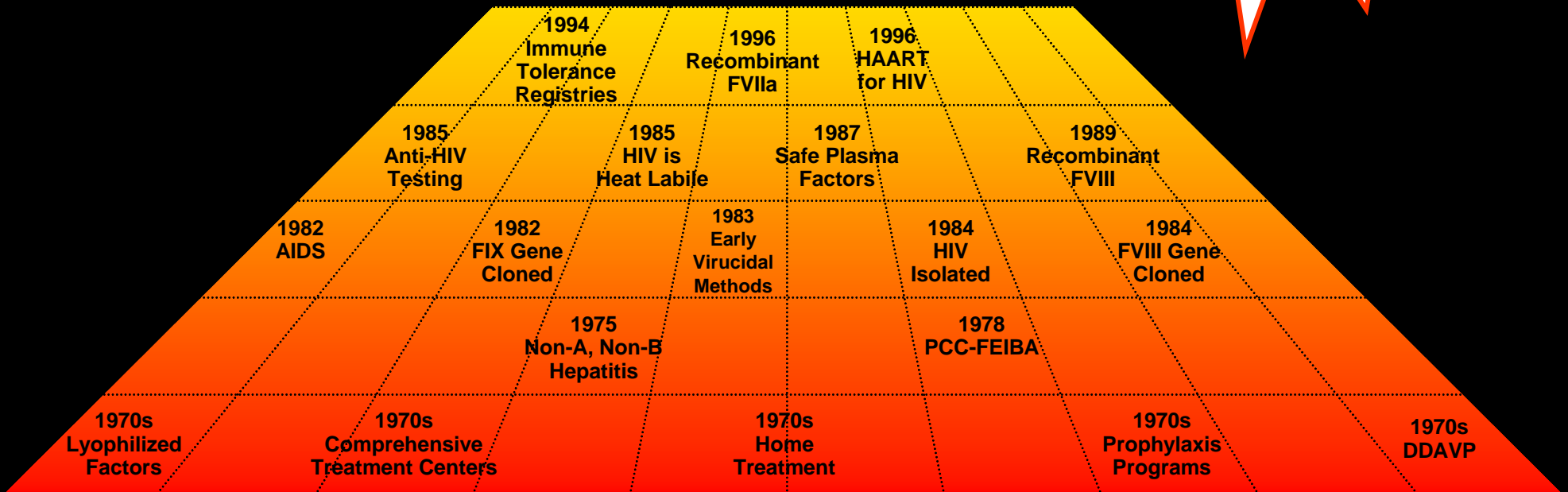
The 1970s: the success story of the decade



The 1970s: the success story of the decade



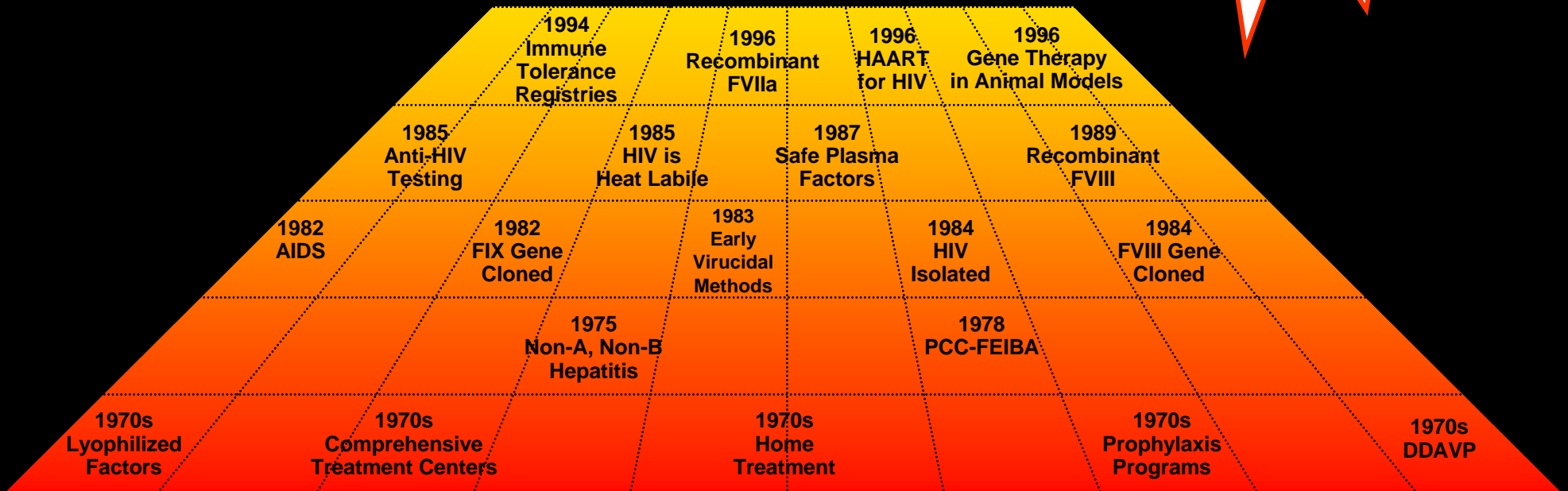
The 1970s: the success story of the decade



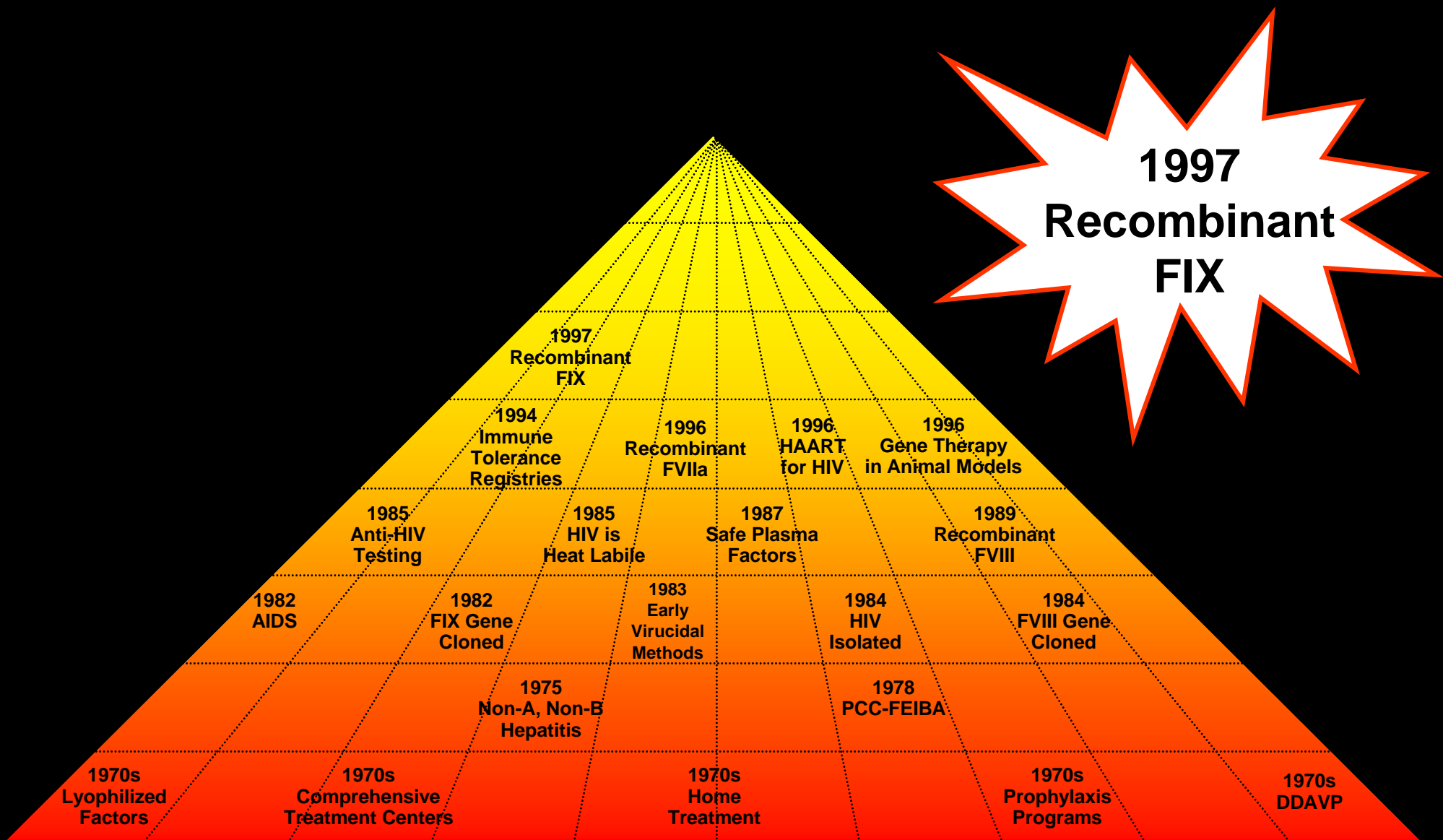
The 1970s: the success story of the decade



**1996
Gene Therapy
in Animal Models**

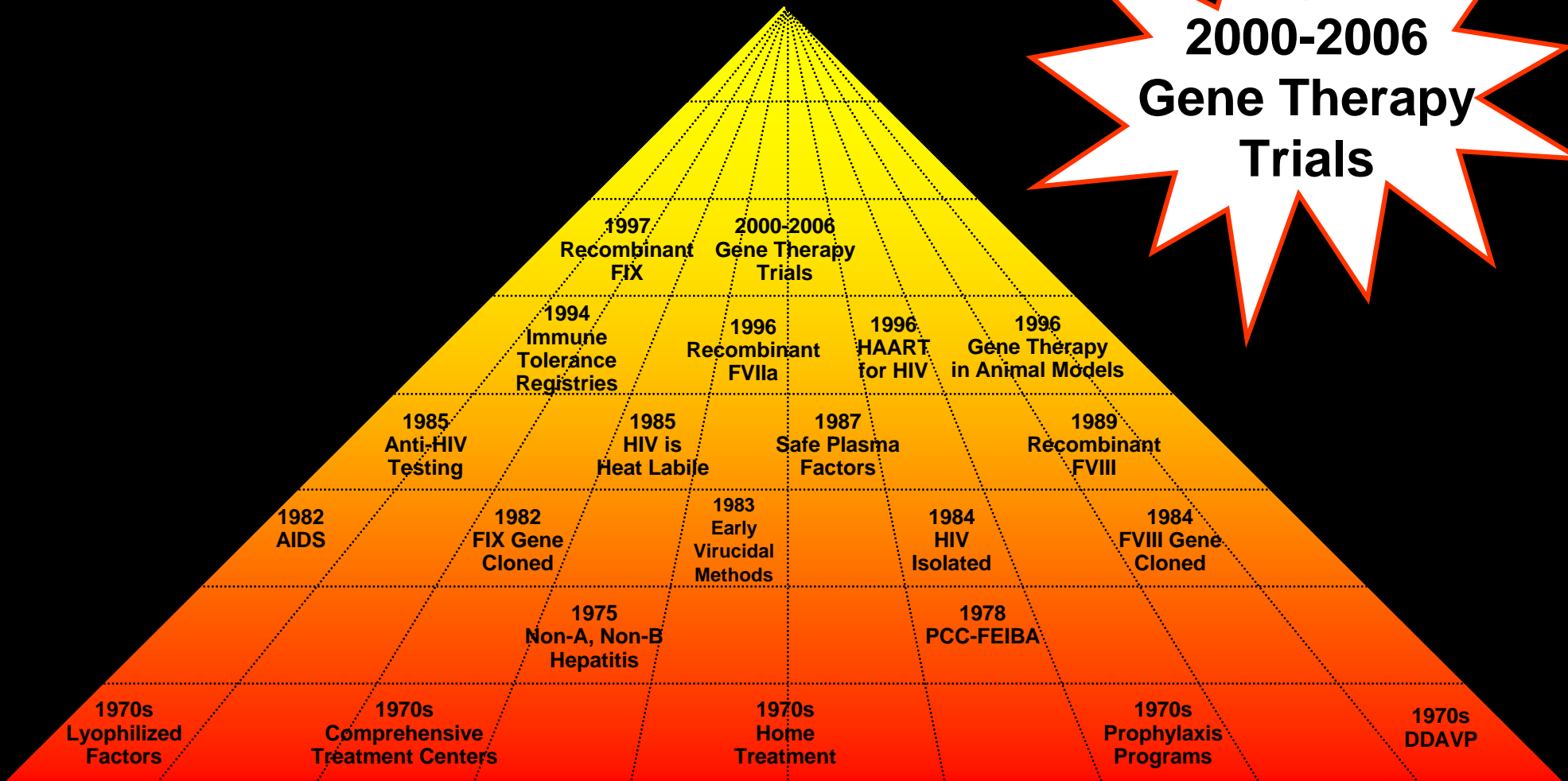


The 1970s: the success story of the decade

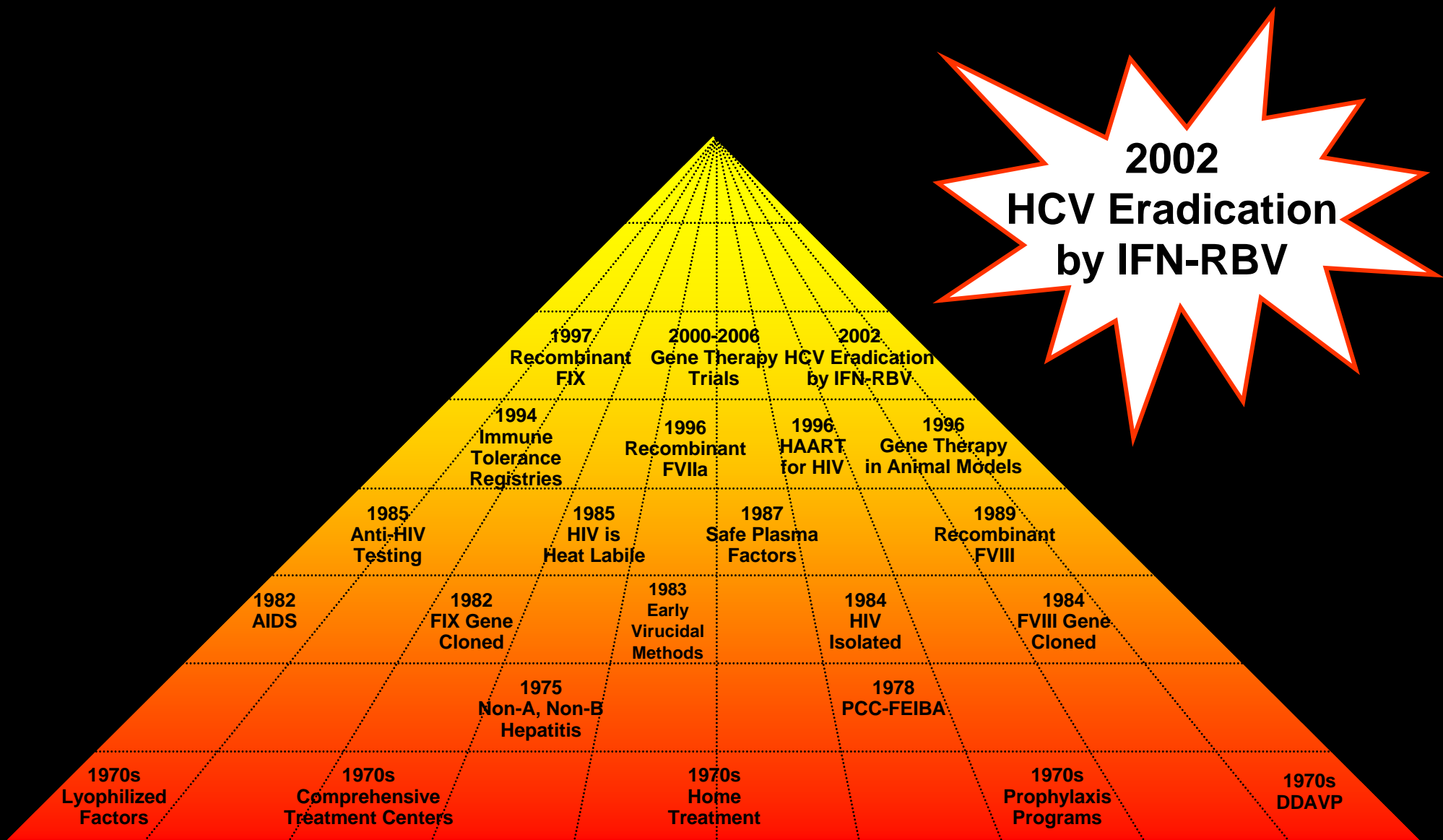


The 1970s: the success story of the decade

2000-2006 Gene Therapy Trials



The 1970s: the success story of the decade



The 1970s: the success story of the decade

WHAT IS NEXT: BUILDING ON STRENGTH

- **More and younger hemophilia experts**
- **Greater and wider factor availability**
- **Improved recombinant products**
- **Less inhibitors, and their improved treatment**
- **Cure of hemophilia: gene transfer therapy**

**MORE AND YOUNGER
HEMOPHILIA EXPERTS**

EDITORIAL

Uncertain times for research on hemophilia and allied disorders

P. M. MANNUCCI and H. R. ROBERTS*

*Editor-in-Chief and *Senior Associate Editor*

”Are we witnessing a dramatic decline in the number of young physicians interested in a clinical and research career in bleeding disorders?”

”...many young hematologists perceive the field of bleeding disorders as being too narrow. This may be overcome by making available training programs in thrombosis...”

LETTERS TO THE EDITOR

Proposal to establish a European Association for Hemophilia and Allied Disorders

C. A. LUDLAM* and P. M. MANNUCCI†, ON BEHALF OF THE INTERDISCIPLINARY WORKING GROUP

*Haemophilia and Thrombosis Centre, Royal Infirmary, Edinburgh, UK; and †Angelo Bianchi Bonomi Haemophilia Centre, Milan, Italy

To cite this article: Ludlam CA, Mannucci PM, on behalf of the Interdisciplinary Working Group. Proposal to establish a European Association for Hemophilia and Allied Disorders. *J Thromb Haemost* 2006; 4: 2270–1.

The establishment of a European Association for Hemophilia and Allied Disorders is proposed. Its aims would be to promote collaboration in clinical practice, research, pharmacovigilance, dissemination of knowledge, education and training. This proposal emanates from an existing broad-based group of European hemophilia physicians as detailed below.

The background for this proposal is that hemophilia is a relatively uncommon condition that is complex and costly to manage effectively. To ensure high quality of treatment it is essential that there is collaboration between all those involved

examples include: PedNet (Pediatric Network of hemophilia centers particularly assessing inhibitor incidence), European Haemophilia Economic Study Group, The von Willebrand disease prophylaxis network (VWD PN), Type 1 VWD project, European Haemophilia Therapy Standardisation Board, and European Study on Orthopaedic Status (ESOS). These collaborations are costly to organize and are partly supported by European Union, but to a large extent funding from the pharmaceutical industry is necessary.

A further group of 45 established European physicians from 16 countries met recently to consider issues that might

EUROPEAN CURRICULUM FOR THROMBOSIS AND HAEMOSTASIS

- 1. Role of Thrombosis & Haemostasis specialist**
- 2. The practice of Thrombosis & Haemostasis**
- 3. Bleeding and thromboembolic disorders**
- 4. Areas of consultative haemostasis**
- 5. Transfusion medicine**

To be published, Haemophilia, 2008

MORE AND YOUNGER HEMOPHILIA EXPERTS: OTHER CURRENT INITIATIVES

- **WFH and NMOs**
- **Medical organizations: EAHAD, HTRS, ATHAN**
- **Industry initiatives: Bayer Awards, Malmö Baxter Workshop**

**GREATER AND WIDER FACTOR
AVAILABILITY**

Current concentrates



- **Recombinant**
 - safe from infection



- **Plasma derived**
 - safe from HIV/HAV/HBV/HCV
 - Probably safe from other infections
 - Continued surveillance - EUHASS

PLASMA FRACTIONATION

- **70 active plants in 1984**
- **30 active plants in 2007**

SPECIFIC REPLACEMENT PRODUCTS FOR RARE COAGULATION DISORDERS

- A neglected issue!

RECOMBINANT FACTORS: WHAT NEXT?

- **Cost decrease**
- **Production in China and India**

IMPROVED RECOMBINANT PRODUCTS

CURRENT TREATMENT

- **FVIII preparations currently have a approximate half-life of only 10 to 12 hours**
- **Potential benefits of long-acting FVIII products:**
 - **Extended protection from bleeding**
 - **Reduced infusion frequency**
 - **May avoid need for central catheter implantation**

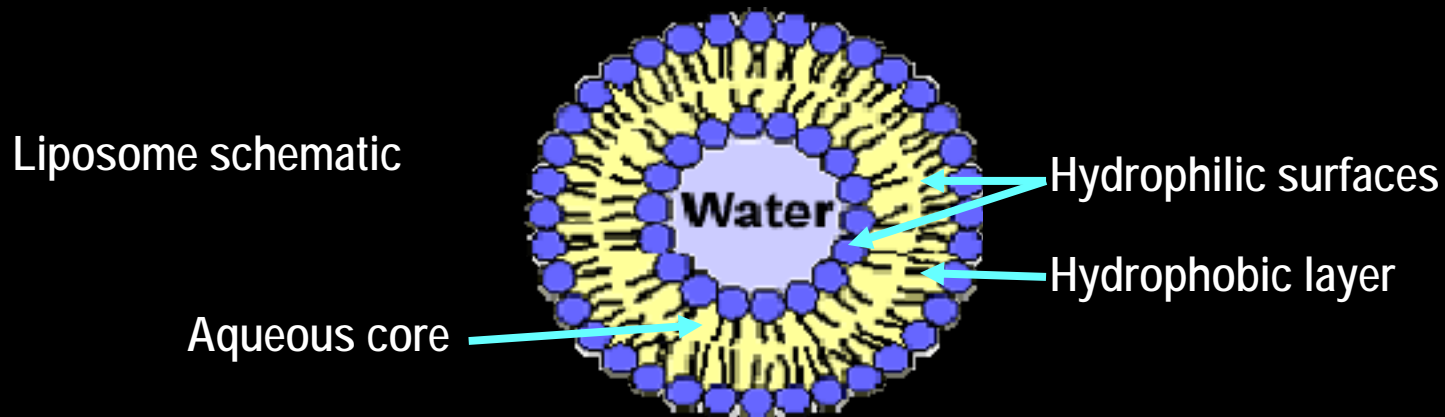
LONG ACTING (LA) RECOMBINANT COAGULATION FACTORS

Multiple strategies

- **Sustained delivery**
 - **PEGylated liposomes (rFVIII)**
- **Chemical modifications**
 - **Site-specific PEGylated rFVIII**
 - **Site-specific PEGylated rFVIIa**
- **Genetic modifications**
 - **Protease-resistant rFVIII**
 - **Receptor-binding alterations to slow FVIII clearance**
 - **rFVIIa analogue with enhanced activity**
- **Fusion with carrier proteins (Fc, Albumin)**
 - **rFVIIa**

PEGylated Liposomes

- **Liposomes are small (~100 nm diameter) lipid vesicles**
 - **Phospholipid bilayer surrounding an aqueous interior**
 - **Liposomes have been effective as drug-delivery vehicles (e.g., doxorubicin, amphotericin B, daunorubicin)**
 - **Rapidly cleared from serum by phagocytic cells**



- **High molecular weight polyethylene glycol (PEG) polymers can extend the circulatory availability**
- **Bayer HealthCare in collaboration with Zilip-Pharma has combined these technologies into a proprietary pegylated liposome (PEGLip)**

OTHER “NEWER” PRODUCTS

- **Coagulation factors from milk of transgenic pigs**
- **High-yield rFIX**
- **FX muteins**
- **Anti-TFPI agents (aptamer and fucoidan)**
- **Anti-APC agents (aptamer)**

**Severe Hemophilia A Therapy
2010?**

**Plasma-derived
FVIII**

**Recombinant
FVIII**

**Recombinant FVIII +
Recombinant VWF**

**FVIII
Conjugates
(eg. PEG)**

**Modified FVIII
(eg. fusion proteins)**



**LESS INHIBITORS AND THEIR
IMPROVED TREATMENT**

CAN WE DECREASE INHIBITOR INCIDENCE IN PREVIOUSLY UNTREATED CHILDREN?

- **Less immunogenic factors**
- **Early implementation of prophylaxis**

TYPE OF REPLACEMENT THERAPY AND INHIBITOR DEVELOPMENT IN CHILDREN

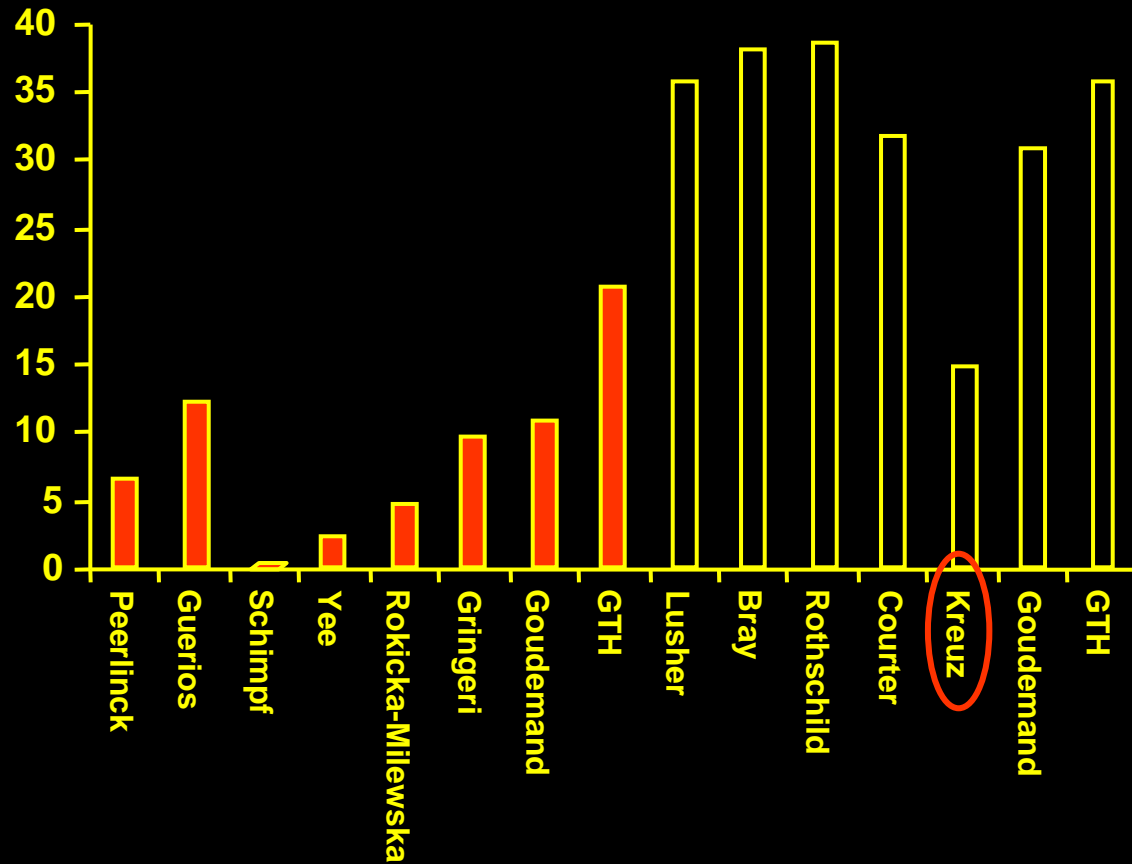
**Inhibitor
Development**

**Inhibitor
Tolerance**

**Influenced by
multiple genetic and exogenous variables**

**? Origin of concentrates ?
? Content of VWF ?**

Cumulative risk of inhibitor development: Single plasma-derived and single recombinant products



Escuriola Ettingshausen & Kreuz,
Haemophilia 2007

Inhibitor cumulative incidence

Observational PUP studies

Non-homogenous study populations

- **Severity (<1/<2%)**
- **mutation type**
- **ethnicity**
- **pre-treatment (PUP,MTP)**
- **therapy regimen**

Non-homogenous study designs

- **prospective/retrospective**
- **frequency and method of inhibitor testing**
- **different observation periods**

Prospective studies needed !
Randomized studies needed !

SUMMARY OF RETROSPECTIVE COHORT STUDIES

- **Goudemand et al (Blood 2006; 107: 46)** found a 2.4 fold greater risk in patients treated with recombinant FVIII than in those treated with a VWF-containing plasma FVIII concentrate
- **Chalmers et al (Haemophilia 2007; 13: 149)** found a 1.8 fold greater risk in patients treated with recombinant FVIII than in those treated with VWF-containing plasma concentrates
- **Gouw et al (Blood 2007)** found no difference in immunogenicity between these two types of FVIII products

Inhibitor incidence with recombinant vs. plasma-derived FVIII in previously untreated patients with severe hemophilia A: homogeneous results from four published observational studies

T. CALVEZ,* Y. LAURIAN† and J. GOUDEMANT‡

J Thromb Haemost 2008; **6**: 390–2.

Measurements of risk (rFVIII vs. pdFVIII) and 95% confidence interval

All inhibitors

Study A
Goudemand *et al.*

Study B *
Escuriola-Ettingshausen & Kreuz

Study C
Chalmers *et al.*

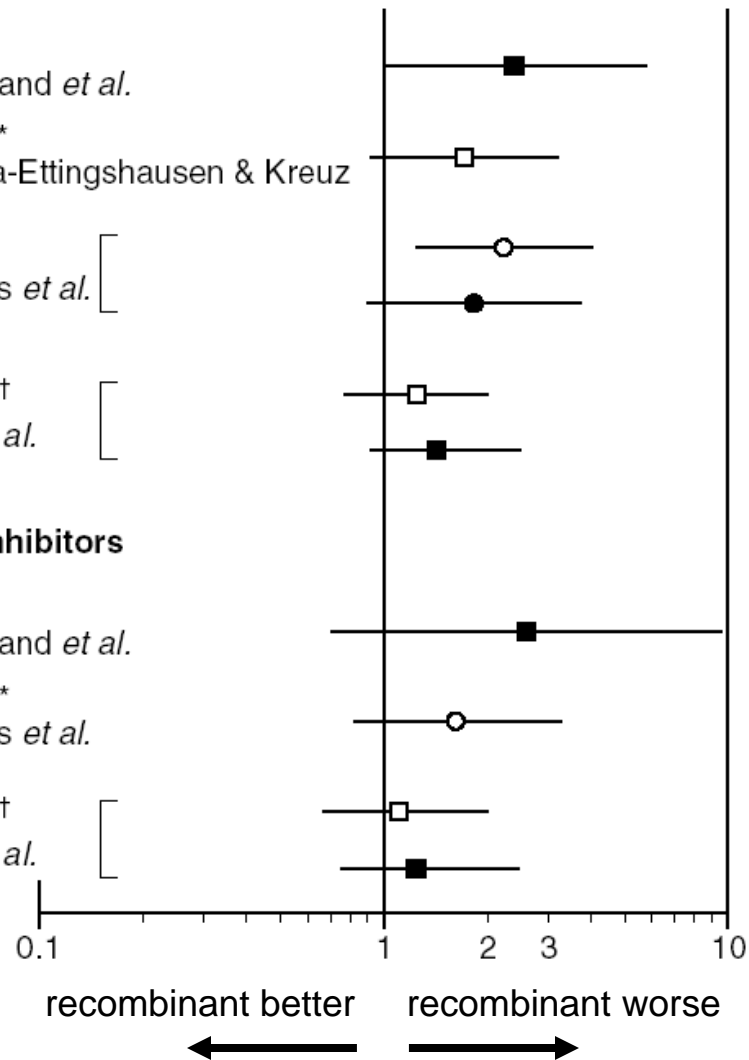
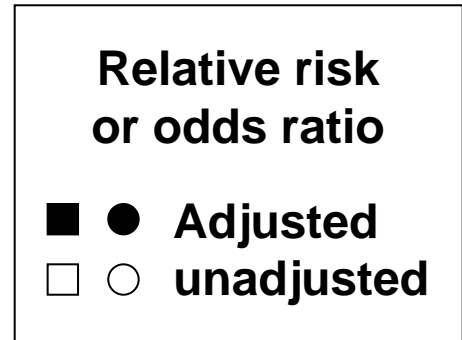
Study D †
Gouw *et al.*

High titre inhibitors

Study A
Goudemand *et al.*

Study C *
Chalmers *et al.*

Study D †
Gouw *et al.*



THE SIPPET STUDY

*P.M. Mannucci, J. Goudemand, A. Gringeri, W.Kreuz,
F. Peyvandi, E. Santagostino*

**Inhibitor Development in Patients Previously
Untreated (PUPs) or Minimally Treated
(MTPs) when Exposed to VWF-Containing
FVIII Concentrates or to recombinant FVIII
concentrates: a randomized clinical trial.**

**Study acronym: SIPPET
(Study on Inhibitors in Plasma-Product Exposed Toddlers)**

BARRIERS TO MULTI-NATIONAL, INDIPENDENT CLINICAL TRIALS

- **Very high cost**
 - **CRO costs, IRB costs, central lab and shipping costs, institutional overheads, product costs**
 - **Difficulty in obtaining independent funding**
- **Local and international over-regulation:**
 - **Ethical committees, IRB**
 - **Indemnity insurance**
 - **Human tissue act. Sample transport regulations**
 - **European Commission and US/Japanese “tripartite” regulations.**
 - **Conduct to GCP/FDA Standard even for non-licensing studies..**
 - **Free products**

**PRIMARY PROPHYLAXIS IN PUPs MAY
DECREASE THE INCIDENCE
OF INHIBITORS**

British Journal of Haematology, 130, 422–427

bjh research paper

Environmental risk factors for inhibitor development in children with haemophilia A: a case–control study

Elena Santagostino,¹ Maria Elisa Mancuso,¹ Angiola Rocino,² Giacomo Mancuso,³ Maria Gabriella Mazzucconi,⁴ Annarita Tagliaferri,⁵ Maria Messina⁶ and Pier Mannuccio Mannucci¹

Recombinant versus plasma-derived factor VIII products and the development of inhibitors in previously untreated patients with severe hemophilia A: the CANAL cohort study

Samantha C. Gouw,^{1,2} Johanna G. van der Bom,³ Günter Auerswald,⁴ Carmen Escuriola Ettinghausen,⁵ Ulf Tedgård,⁶ and H. Marijke van den Berg,¹ for the CANAL Study group

BLOOD, 1 JUNE 2007 • VOLUME 109, NUMBER 11

Haemophilia (2005), 11, 79–83

DOI: 10.1111/j.1365-2516.2005.00921.x

Prophylactic treatment effects on inhibitor risk: experience in one centre

M. MORADO, A. VILLAR, V. JIMÉNEZ YUSTE, M. QUINTANA and F. HERNANDEZ NAVARRO
Congenital Coagulopathy Section, Haematology Service, University Hospital 'La Paz', Madrid, Spain

IMPROVED TREATMENT OF INHIBITORS

- **Eradication through immune tolerance**
- **Improved treatment of bleeding with bypassing agents**
 - **Optimal dosing**
 - **Secondary prophylaxis**

IMMUNE TOLERANCE IN INHIBITOR PATIENTS (randomized trials)

- ITI study
high dosage FVIII (200 U/kg/day)
VS
low dosage FVIII (50U/kg thrice weekly)
- RESIST study (in poor-prognosis patients)
recombinant FVIII
VS
plasma-derived VWF-FVIII

DOSING REGIMENS OF NOVOSEVEN

Randomized trial

- **Single 270 $\mu\text{g kg}^{-1}$ dose is as effective and safe as three 90 $\mu\text{g kg}^{-1}$ doses for the treatment of joint bleeding**

Kavakli et al, Thromb Haemost 2006

Santagostino et al. J Thromb Haemost, 2006

Young et al, Haemophilia, 2007

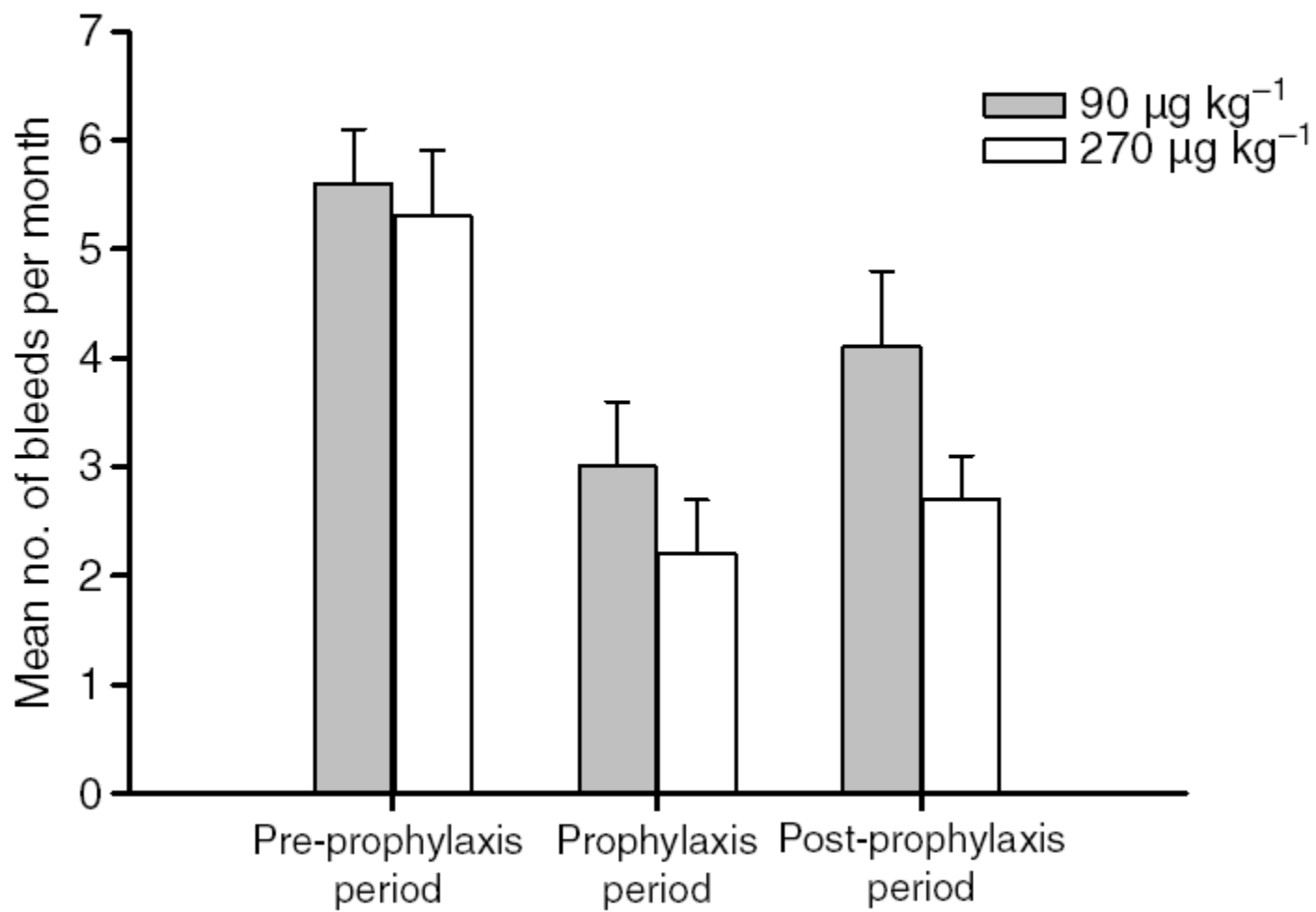
SECONDARY PROPHYLAXIS IN INHIBITOR PATIENTS

- **Randomized crossover ProFEIBA trial**
- **Randomized, crossover, double-blind NovoSeven trial**

ORIGINAL ARTICLE

Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors

B. A. KONKLE,* L. S. EBBESEN,† E. ERHARDTSEN,† R. P. BIANCO,‡ T. LISSITCHKOV,§ L. RUSEN¶ and M. A. SERBAN**



TOWARDS CURE?

GENE TRANSFER THERAPY

The recent past as a prologue

- **Outstanding preclinical success during the past 10 years, but**
- **Six clinical trials in HA and HB failed to demonstrate long-term hemostatic benefit**
- **Host innate and adaptive immune response to gene vectors were the most important obstacles**

GENE TRANSFER THERAPY

What next?

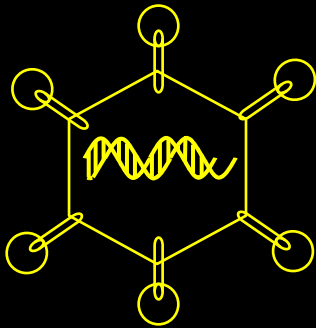
- **Two clinical studies will start soon in HB (gene transfer by AAV vectors)**
- **In one of these studies, the vector is co-administered with immunosuppression**

FUTURE APPROACHES

- **Non-viral DNA vectors**
- **DNA microparticles**
- **Transposon-based delivery systems**
- **miRNA approach**
- **Transgene expression in platelet and EC lineages**

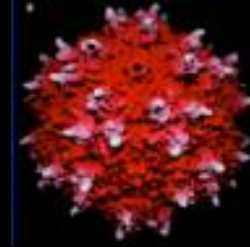
PRESENT AND FUTURE TRANSFER TECHNOLOGY PLATFORM

High-capacity Adenoviral



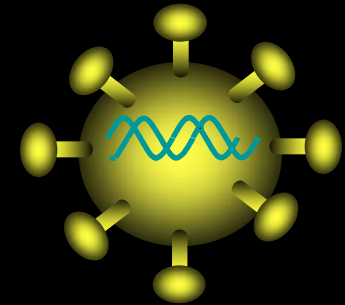
Chuah et al., Blood 2003

AAV



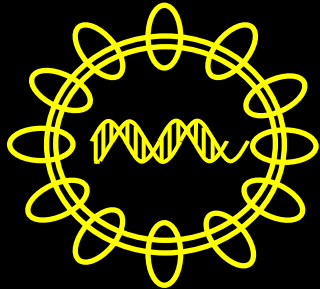
VandenDriessche et al., JTH 2007

Lentiviral / Retroviral



VandenDriessche et al., PNAS 1999
Van Damme et al., Stem Cells, 2006
VandenDriessche et al., Blood 2002

Nanoparticles



Yamada et al., Nat Biotech, 2003

Non-viral: transposon

Chuah et al, in prep, 2008



bioengineered
muscle implants

Thorrez et al., Mol.Ther., 2006
Biomaterials, 2008

Severe Hemophilia A Therapy 2018

Plasma-derived
FVIII

Recombinant
FVIII

Recombinant FVIII +
Recombinant VWF

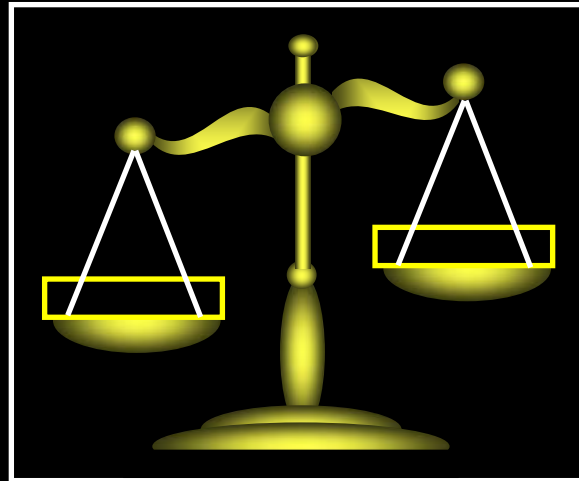
FVIII
Conjugates
(eg. PEG)

Modified FVIII
(eg. fusion proteins)

In vivo gene transfer
(viral vector mediated)

Ex vivo gene transfer
(adult stem cell-based)

GENE THERAPY FOR HEMOPHILIA



BENEFIT

**LONG-TERM
THERAPEUTIC EFFECT:
CURE?**

RISK

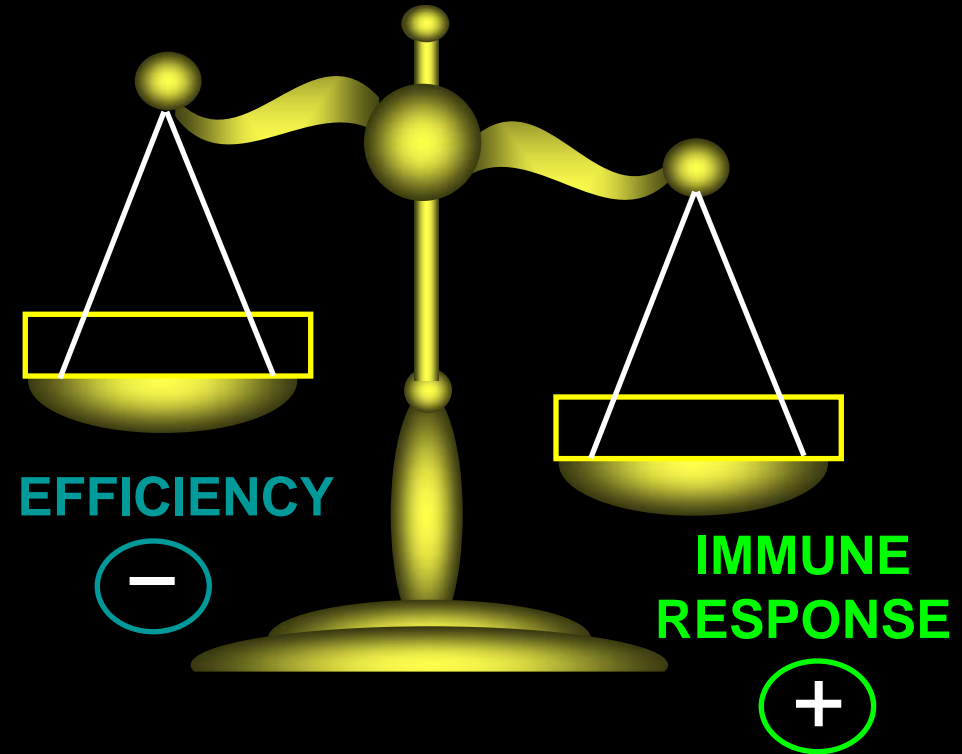
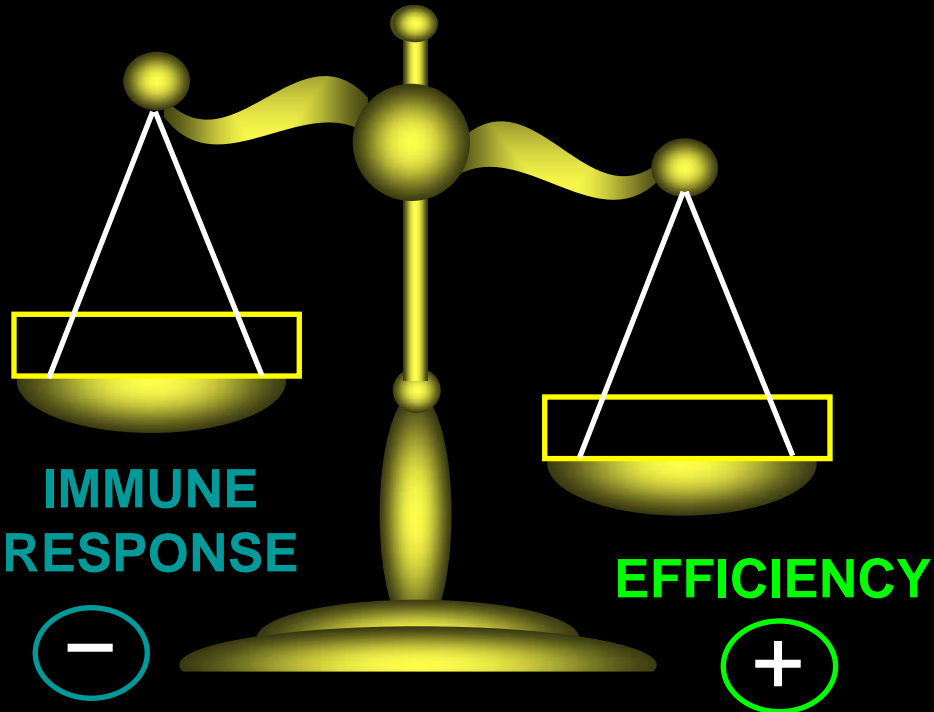
IMMUNE RESPONSE:

- **CLOTTING FACTORS**
- **VECTOR**
- **FVIII/FIX-PRODUCING CELLS**

VIRAL VECTOR



NON-VIRAL VECTOR



How to make non-viral vectors more efficient?

There is always one moment in childhood when a door opens and lets the future in

(Graham Green)

