Gene Therapy for Fanconi Anemia

Jennifer E. Adair, Ph.D.

Fred Hutchinson Cancer Research Center

Hans-Peter Kiem Laboratory

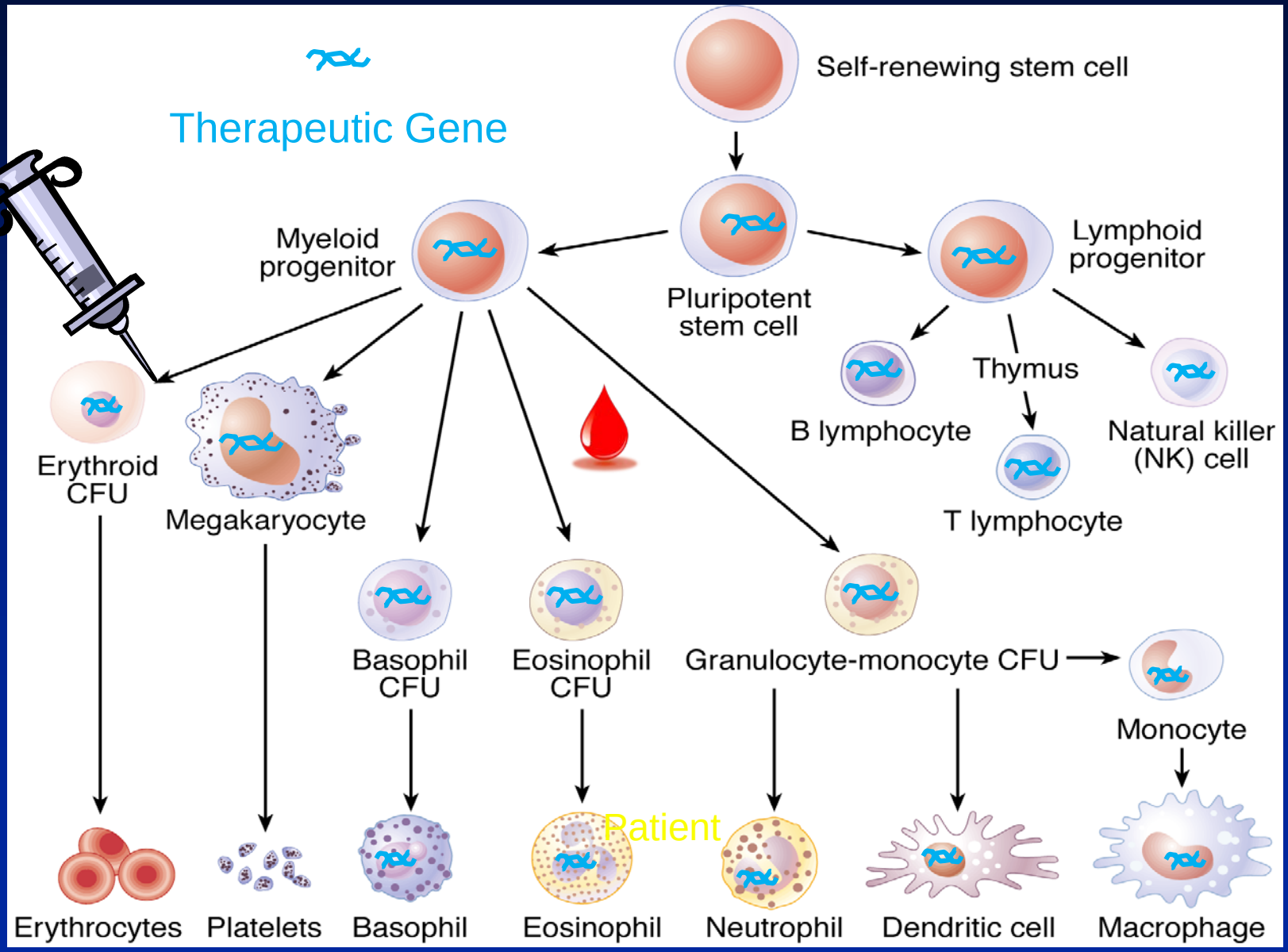
Seattle, Washington, United States

What is Gene Therapy?

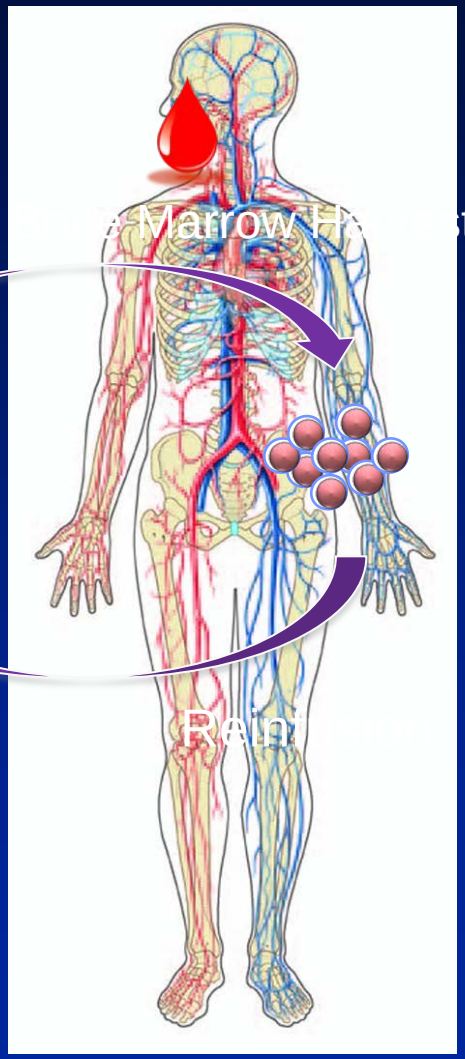
Any therapy where the benefit is achieved by the transfer of genetic material (a “gene”) into a patient’s cells.

For FA patients, the primary goal of gene therapy is to prevent bone marrow failure without the risk of GVHD.

Gene Therapy in Blood Stem and Progenitor Cells

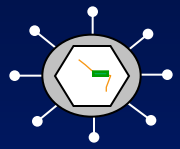


Ex Vivo Gene Therapy: Putting Functional Genes Into Bone Marrow Stem Cells Outside of the Body

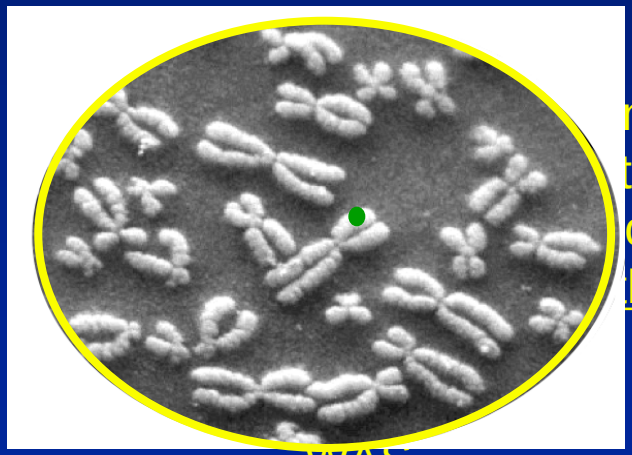


FA Patient

Virus-Mediated Gene Transfer of Functional FA Gene



Isolation of Bone Marrow Stem Cells

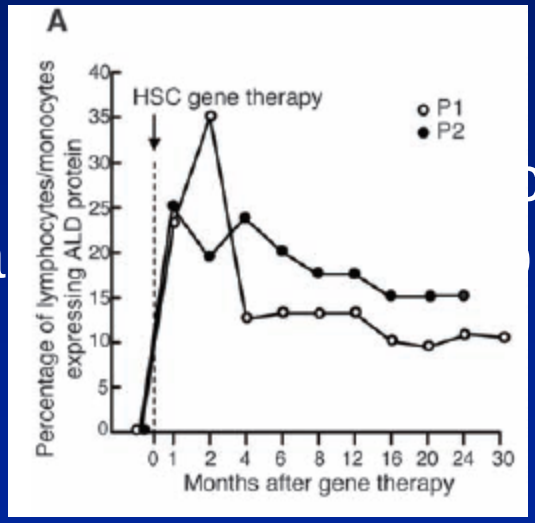


- WAS
- ALD
- MLD

Potential for Success of Gene Therapy in FA Patients

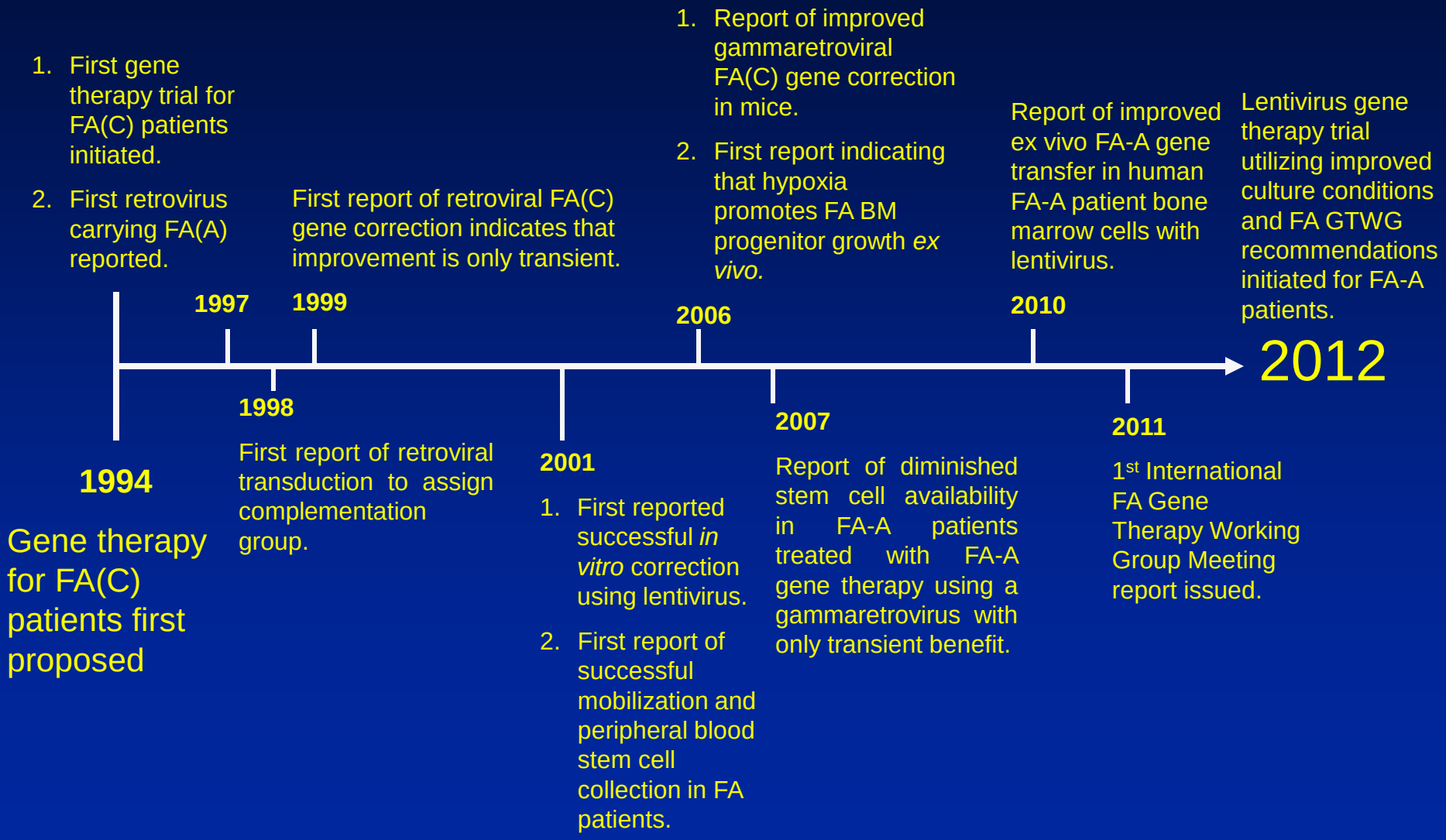
1. Successful gene therapy for other monogenic diseases demonstrates ex vivo gene therapy of bone marrow stem cells can work (SCID-ADA, X-linked SCID, ALD and MLD).

2. Rare evidence [illegible]cism in Fanconi anemia: natura[illegible]roves marrow function.



Cartier *et al.* 2009, *Science*

Clinical Study of FA Gene Therapy: A History



Previous Trials: Outcomes

1. 1999 (Liu) Gammaretretroviral-mediated delivery of FA(C) gene into CD34+ HSCs in FA(C) patients.

   - no long-term engraftment observed; published report

2. 2000 (Wagner) Retro-viral-mediated delivery of FA(C) gene into mobilized peripheral blood HSCs.

   - poor mobilization and blood stem cell survival *ex vivo*; no report

3. 2006 (Williams) Gammaretroviral-mediated gene delivery of FA(A) to CD34+ BM HSCs in FA(A) patients.

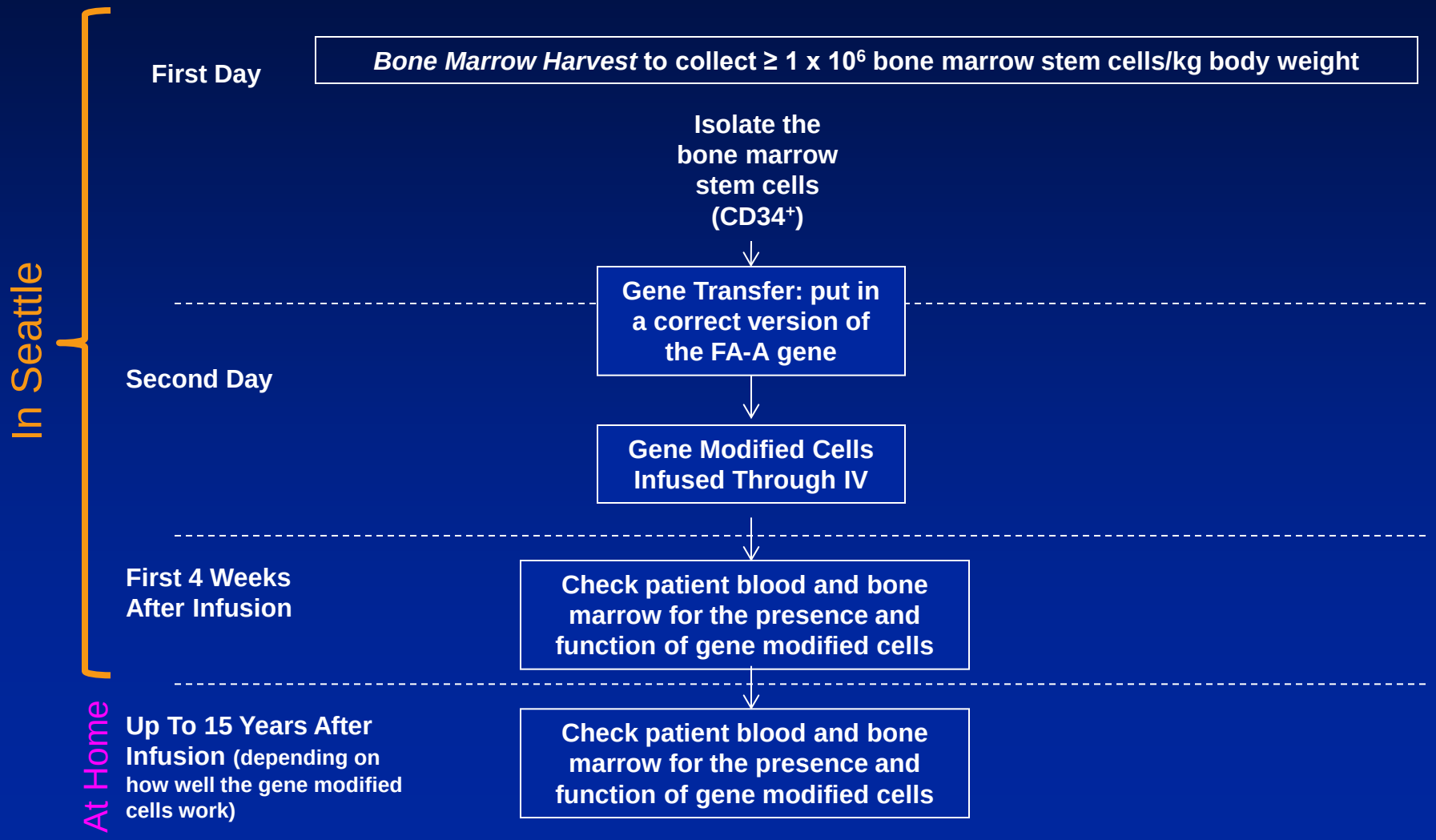
   - transient gene correction; published report

Advances in Gene Transfer Process Should Improve Safety and Engraftment

1. Improved *ex vivo* culture conditions
   - Hypoxia (1-5% O_2)
   - Antioxidant co-culture
2. Improved lentiviral vector design
   - SIN (self-inactivating) to prevent turning on harmful genes nearby
   - Successful and safe in gene therapy for other genetic diseases
3. Shorter transduction protocol
   - Shorter *ex vivo* culture time = greater potential to make new blood cells

Phase I: Study of Gene Transfer for Patients with Fanconi Anemia Complementation Group A (FANCA).

FA-A patients (≥ 4 years) with confirmed FA of the A complimentation group



What We Hope To Learn:

1. Can we collect enough stem cells?

2. Do the improved culture conditions and reduced time outside the body allow for better engraftment?
   - If not, we will try low-dose conditioning

3. Do the gene corrected stem cells produce blood cells after infusion?

4. How safe is this approach in FA-A patients?

Who Can Enroll?

FA-A patients ≥ 4 years old who meet the following criteria:

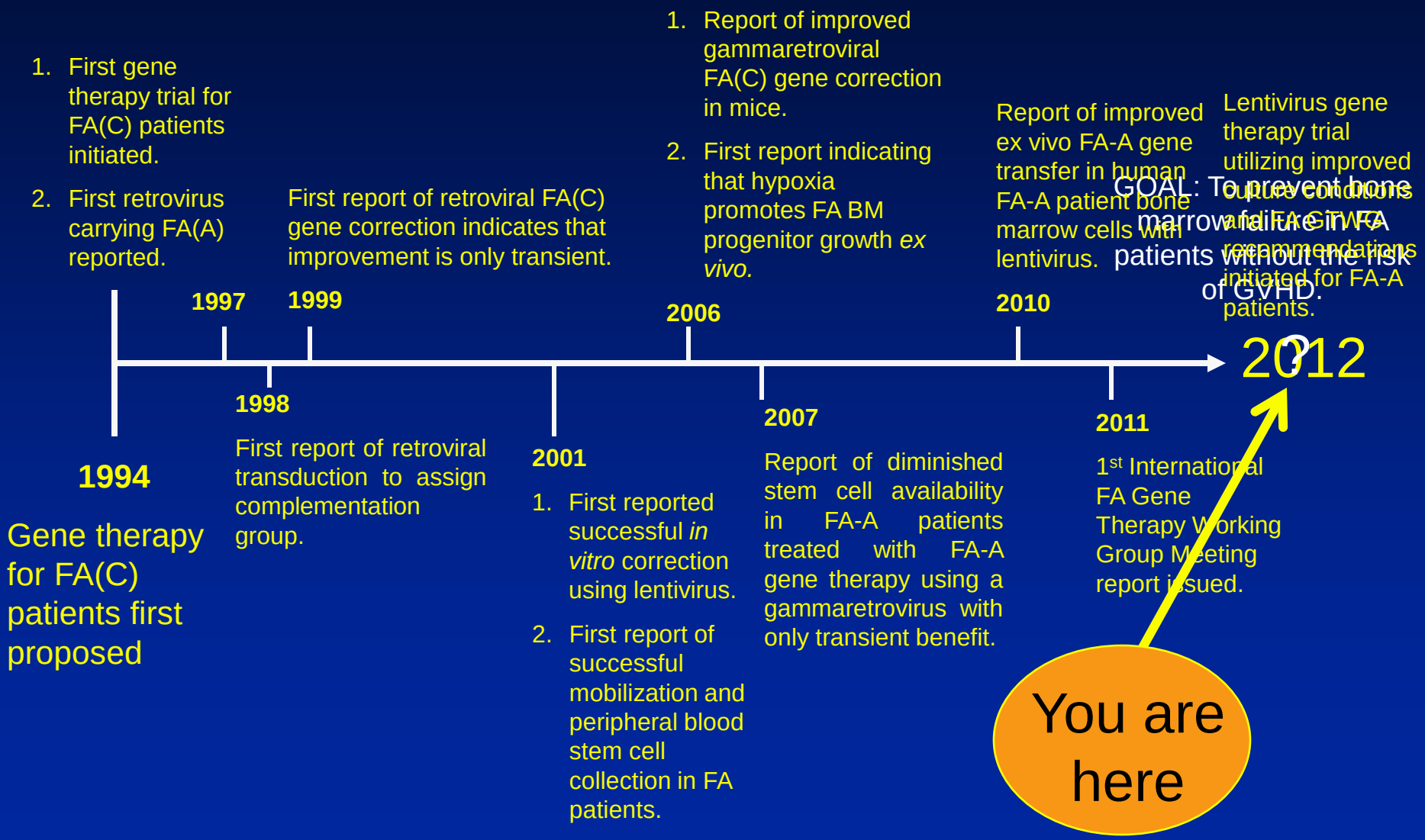
- have normal or near-normal kidney, liver and lung function
- have normal or near-normal bone marrow cytogenetics
- have adequate blood cell counts
  - ANC ≥ 500/mcL
  - Hemoglobin ≥ 8 g/dL
  - Platelets ≥ 20,000/mcL
- are able to understand the consent form or have a parent/legal guardian who understands the consent form
- do not have an active or ongoing infection
- do not have another cancer with limited survival (<2 years)
- do not have another significant disease such as uncontrolled diabetes or heart disease or haemophilia
- not pregnant or HIV+
- not undergoing a BMT with a matched sibling donor

What Can I Expect if I Enroll?

1. Travel to and from Seattle, Washington.
2. ~6 weeks in Seattle:
    a. Testing before treatment if needed (1-2 weeks).
    b. Bone marrow collection and infusion of gene modified cells (2-days).
    c. Post-infusion monitoring including regular blood draws and one bone marrow aspirate after infusion of gene modified cells (4 weeks).
3. Monitoring after returning home (done locally):
    a. For the first 2 months, blood draws every two weeks.
    b. For the next 9 months, blood draws once per month.
    c. If gene modified cells are found in blood at 1 year, blood draws at least annually; bone marrow samples if needed.

Costs: All study-related treatments while in Seattle are covered by the clinical trial. Any treatments that are standard for FA are still covered by patients and/or their insurance carrier. Travel and lodging for time in Seattle are not covered by the study, but FARF can help!

Why Should I Participate?



Thank You for Your Attention!

Lentivirus-Mediated FA-A Gene Delivery