Gene Therapy for Fanconi Anemia: The Second Decade and Beyond

Jennifer E. Adair, Ph.D.

Fred Hutchinson Cancer Research Center

Hans-Peter Kiem Laboratory

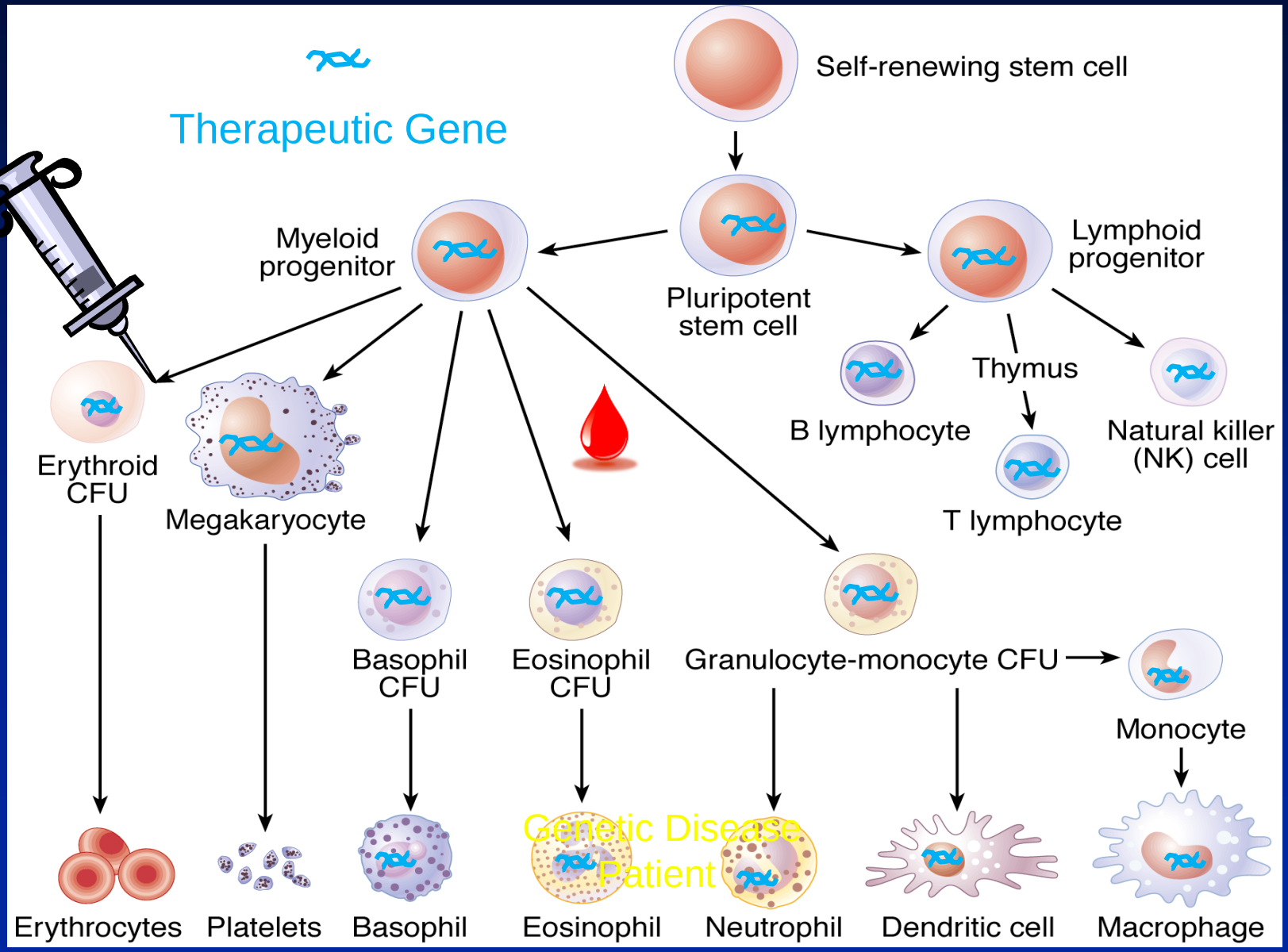
Seattle, Washington, United States

What is Gene Therapy?

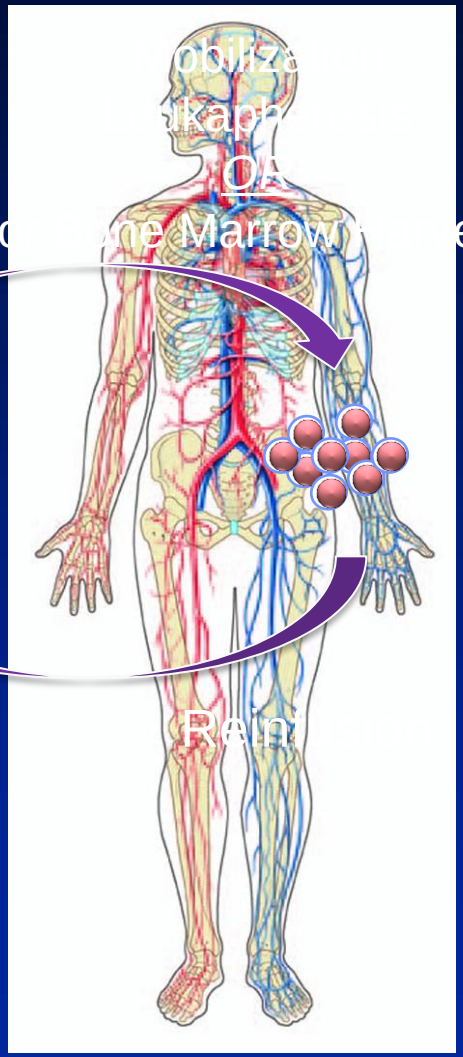
Any therapy where the benefit is achieved by the transfer of genetic material (a “gene”) into a patient’s cells.

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

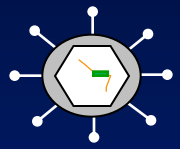


Ex Vivo Gene Therapy: Putting Functional Genes Into Bone Marrow Stem Cells Outside of the Body



FA Patient

Virus-Mediated Gene Transfer of Functional FA Gene



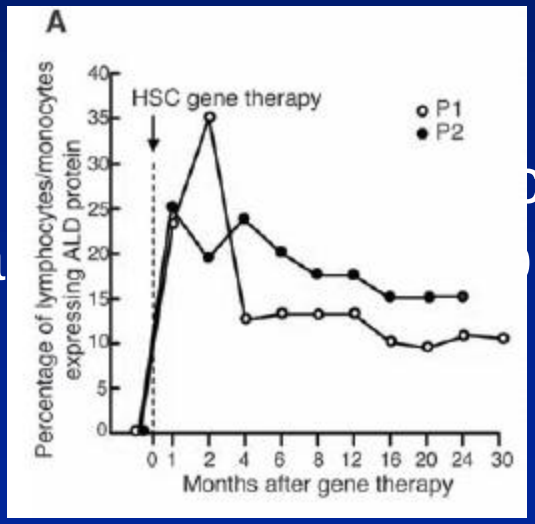
Isolation of Bone Marrow Stem Cells

- WAS
- ALD
- MLD

Potential for Success of Gene Therapy in FA Patients

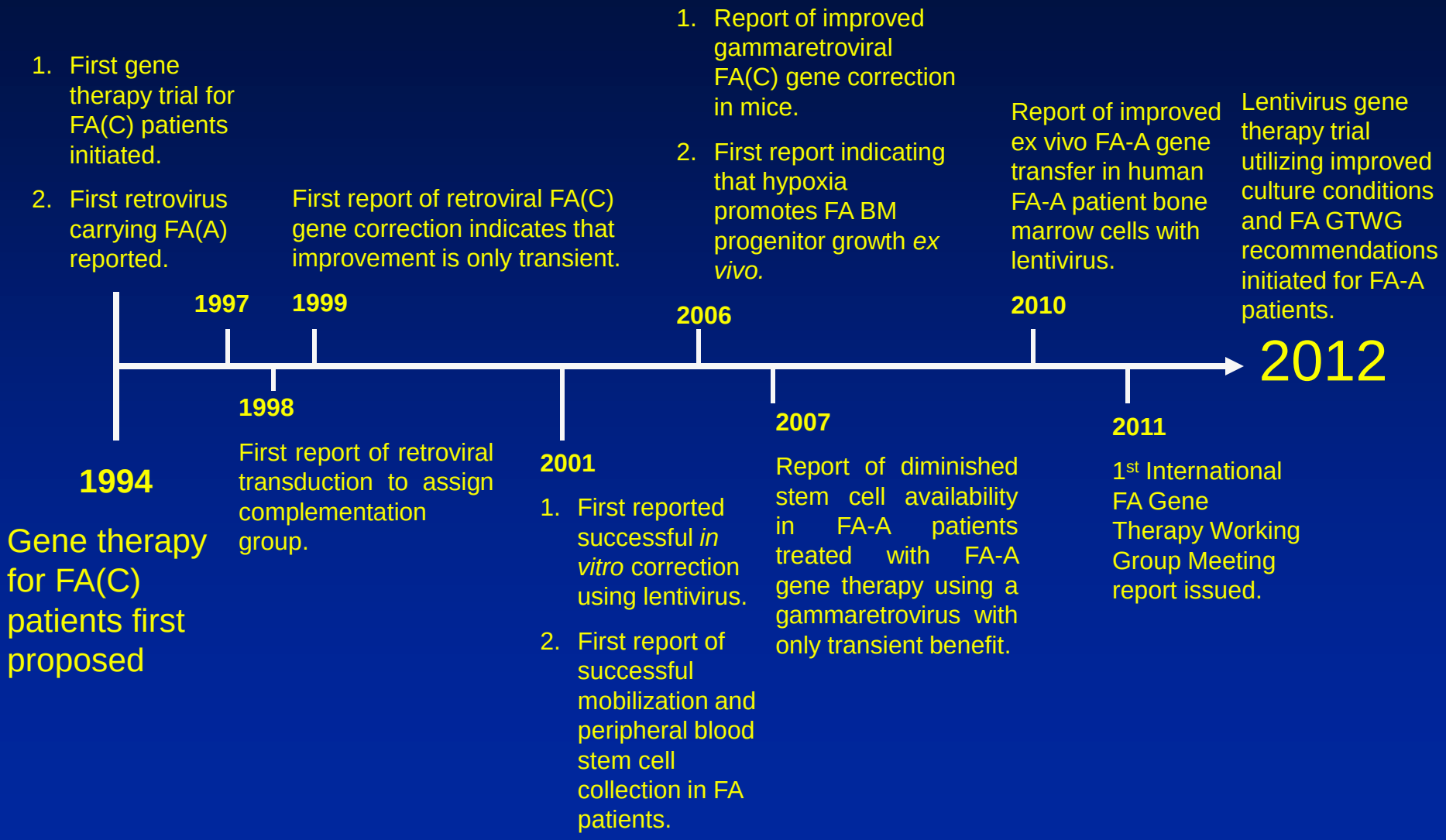
1. Successful gene therapy for other monogenic diseases demonstrates ex vivo gene therapy of bone marrow stem cells can work (SCID-ADA, X-linked SCID, ALD and MLD).

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 results

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

FA gene therapy in the clinic: 18 Years of Research

1. No Phase II Trials primarily due to lack of long-term engraftment in Phase I studies.

   Conditioning or selection of corrected cells?

   - Cyclophosphamide, irradiation or busulfan at low doses may improve engraftment.

2. Low FA patient bone marrow cellularity prevents collection of large numbers of stem cells.

   Can we increase the number of FA blood stem cells?

   - New drugs improve mobilization and stem cell collection.
   - Small molecules or other special cell cultures which increase the number of stem cells may work for FA stem cells after they are corrected.

3. *Ex vivo* culture time and conditions can damage cells further, compromising engraftment potential.

   Can we preserve the engraftment potential of FA blood stem cells?

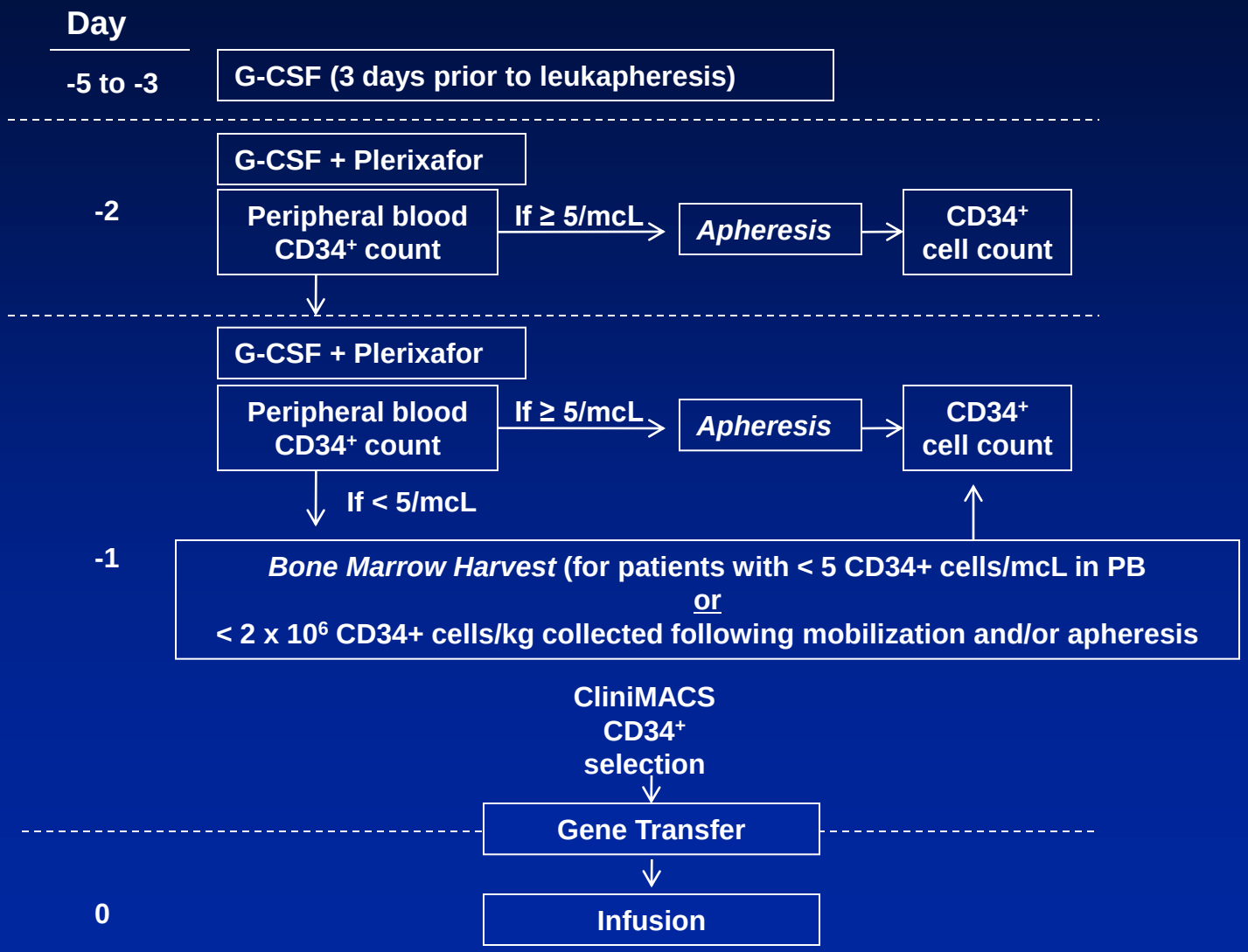
   - Low oxygen and agents that reduce damage caused by oxygen can prevent stem cell damage.
   - Lentivirus vectors reduce the time in culture by ½.

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
3. Shorter transduction protocol
   - Shorter *ex vivo* culture time = greater cell viability and long-term repopulating potential

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

Adult patients (≥ 18 years) with confirmed FA of the A complimentation group



What We Hope To Learn:

1. Can we collect enough stem cells?

2. Does the lentivirus effectively transfer the FA-A gene?

3. Do the improved culture conditions and reduced time outside the body allow for better engraftment?

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

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

Who Can Enroll?

FA-A patients ≥ 18 years old who meet the following criteria:

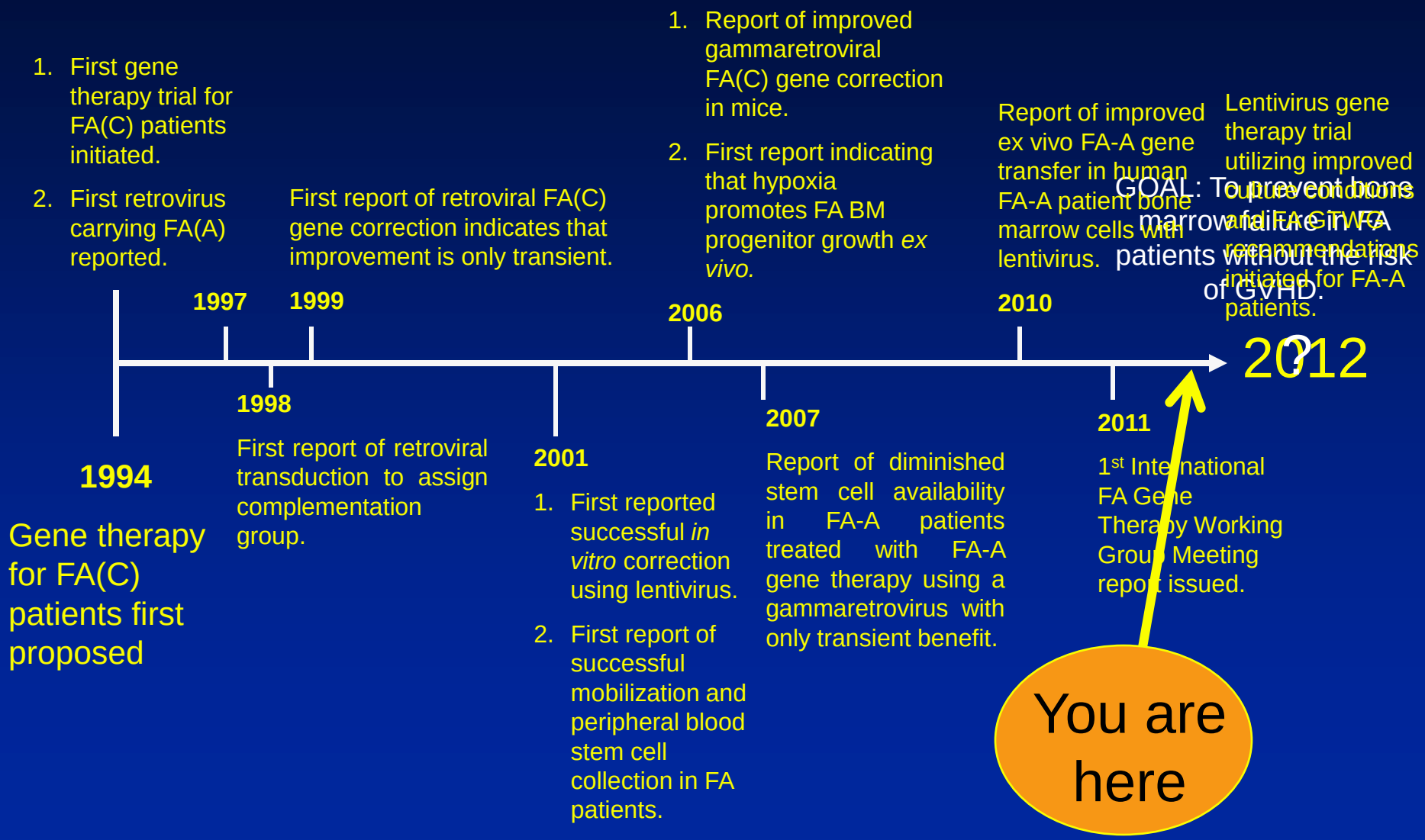
- have normal or near-normal kidney, liver and lung function
- have normal or near-normal bone marrow cytogenetics
- have adequate blood cell counts
  - ANC ≥ 500/mcL
  - Hemoglobin ≥ 8 g/dL
  - Platelets ≥ 20,000/mcL
- are able to take care of themselves and understand the consent form
- do not have 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. ~6-8 weeks in Seattle:
    a. Testing before treatment and placement of a central venous catheter (1-2 weeks).
    b. Treatment for mobilization, collection and infusion (1-2 weeks).
    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.

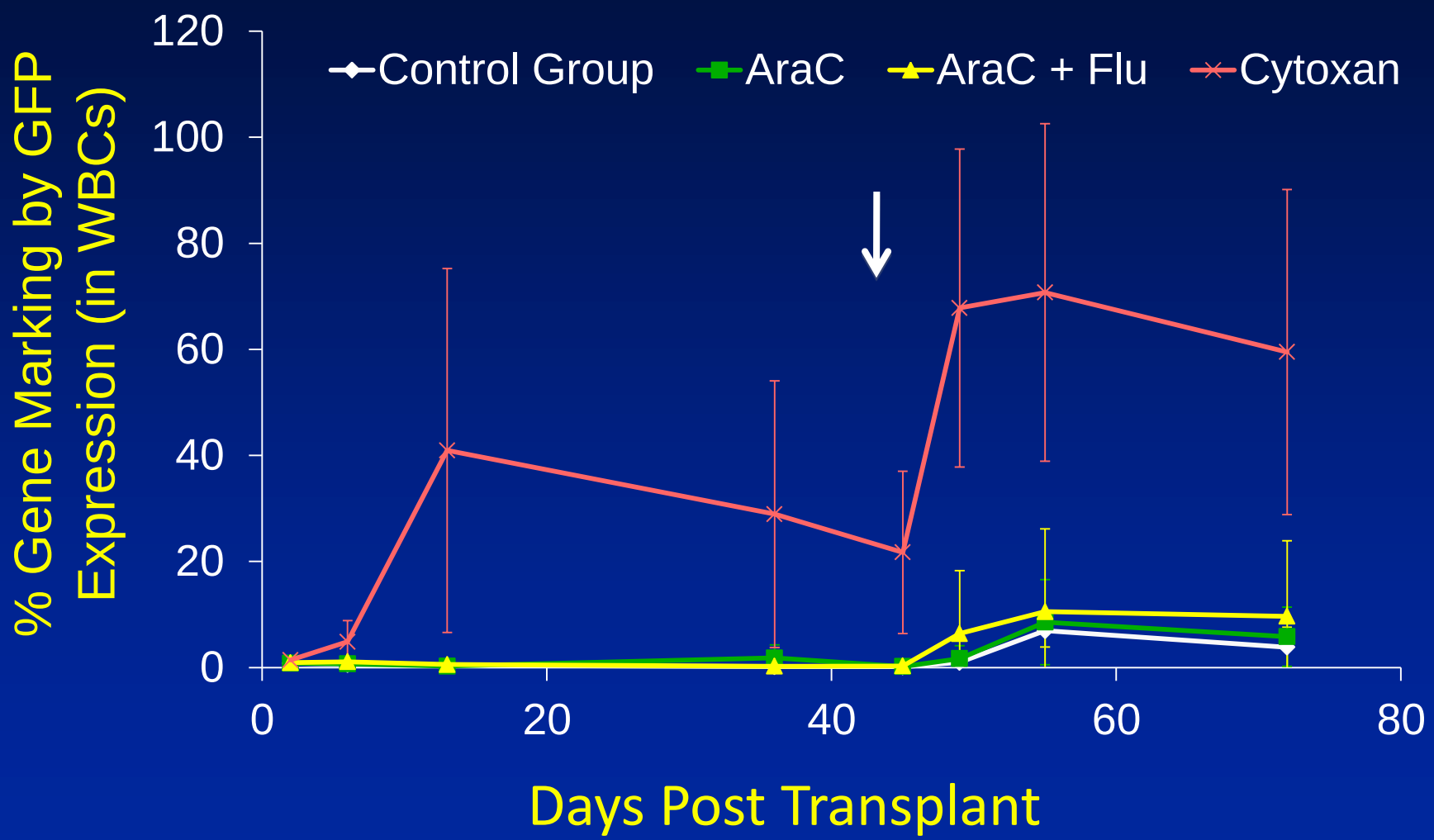
Costs: All study-related treatments while in Seattle are covered by the clinical trial. Any treatments that are standard for FA are still covered by patients and/or their insurance carrier. Travel and lodging for time in Seattle are not covered by the study, but FARF can help!

Why Should I Participate?



Thank You for Your Attention!

Peripheral Blood Gene Marking Detectable Only in Cyclophosphamide-Conditioned Mice

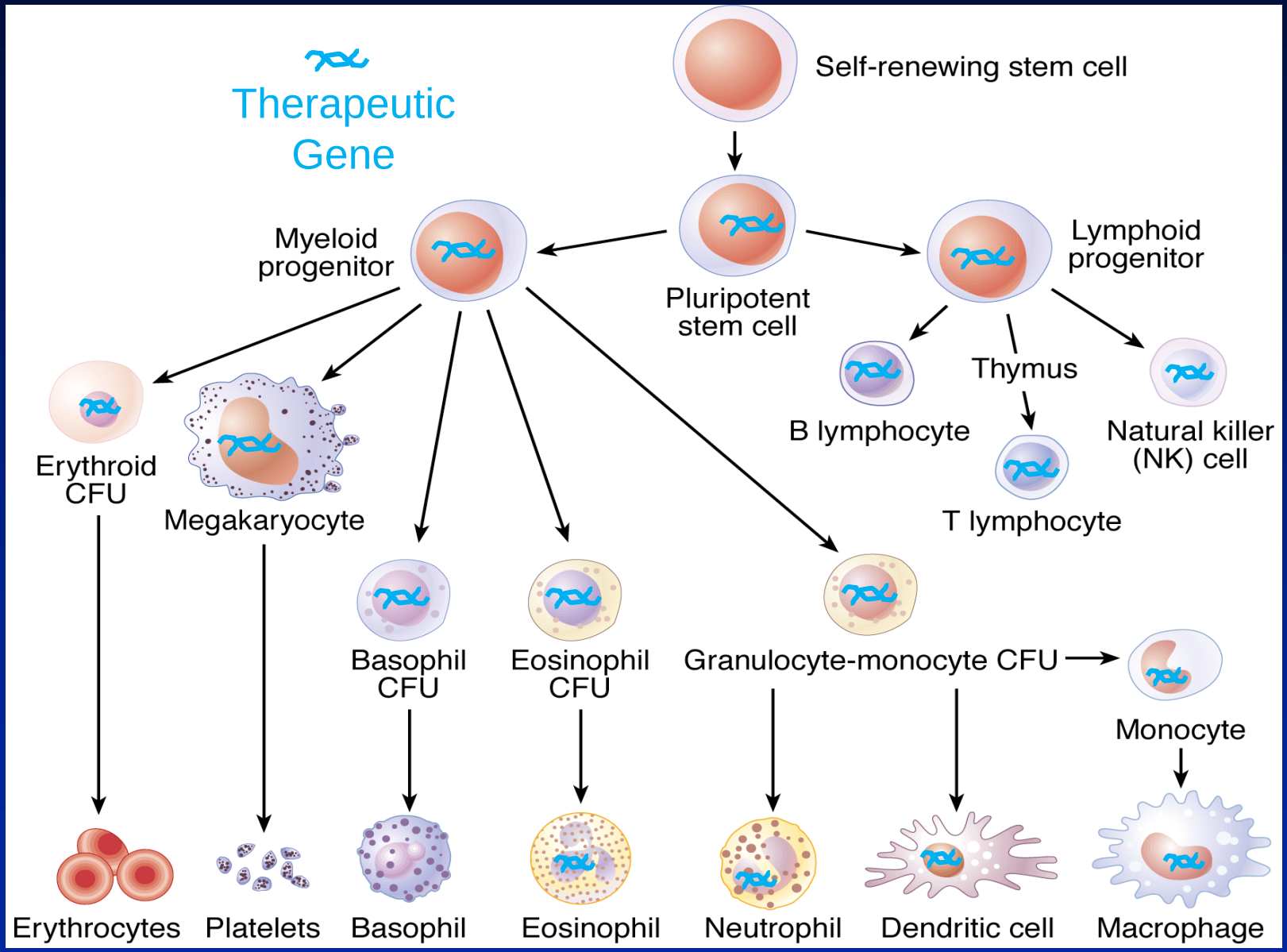


GVHD is Caused by Donor Immune Cells

1. Don't use donor cells: "Fix" the patient's own bone marrow stem cells by giving them a working version of the defective FA gene.

2. Get rid of the donor immune cells if they cause problems: Give donor immune cells a gene that will cause them to die if they misbehave after transplant.

Gene Therapy of Other Cell Types Could Also Benefit FA Patients



T & NK Cell Gene Therapy in Donor Cells: Suicide genes to eliminate GVHD

Retrovirus-Mediated FA Gene Delivery