CIRM Regenerative Medicine Consortium Roundtable

Best Practices in Clinical Design

HIV/AIDS Stem Cell-Based Therapy Overview: Challenges to the Field

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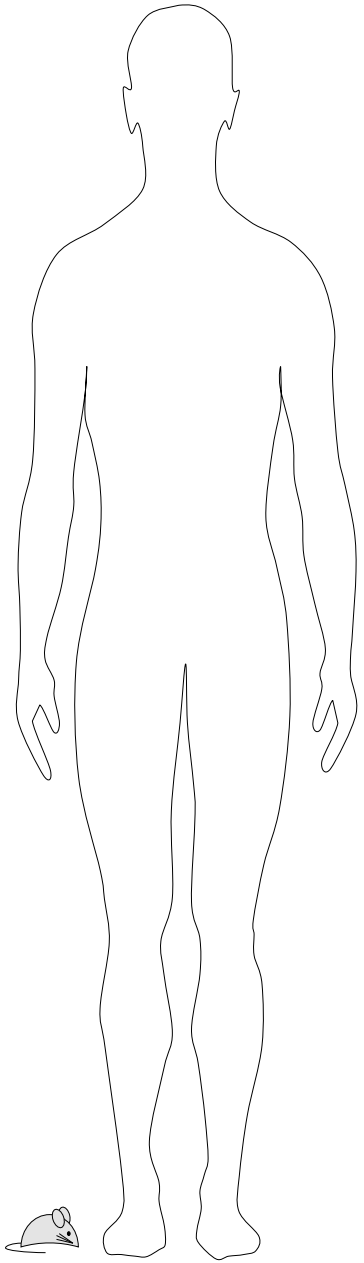
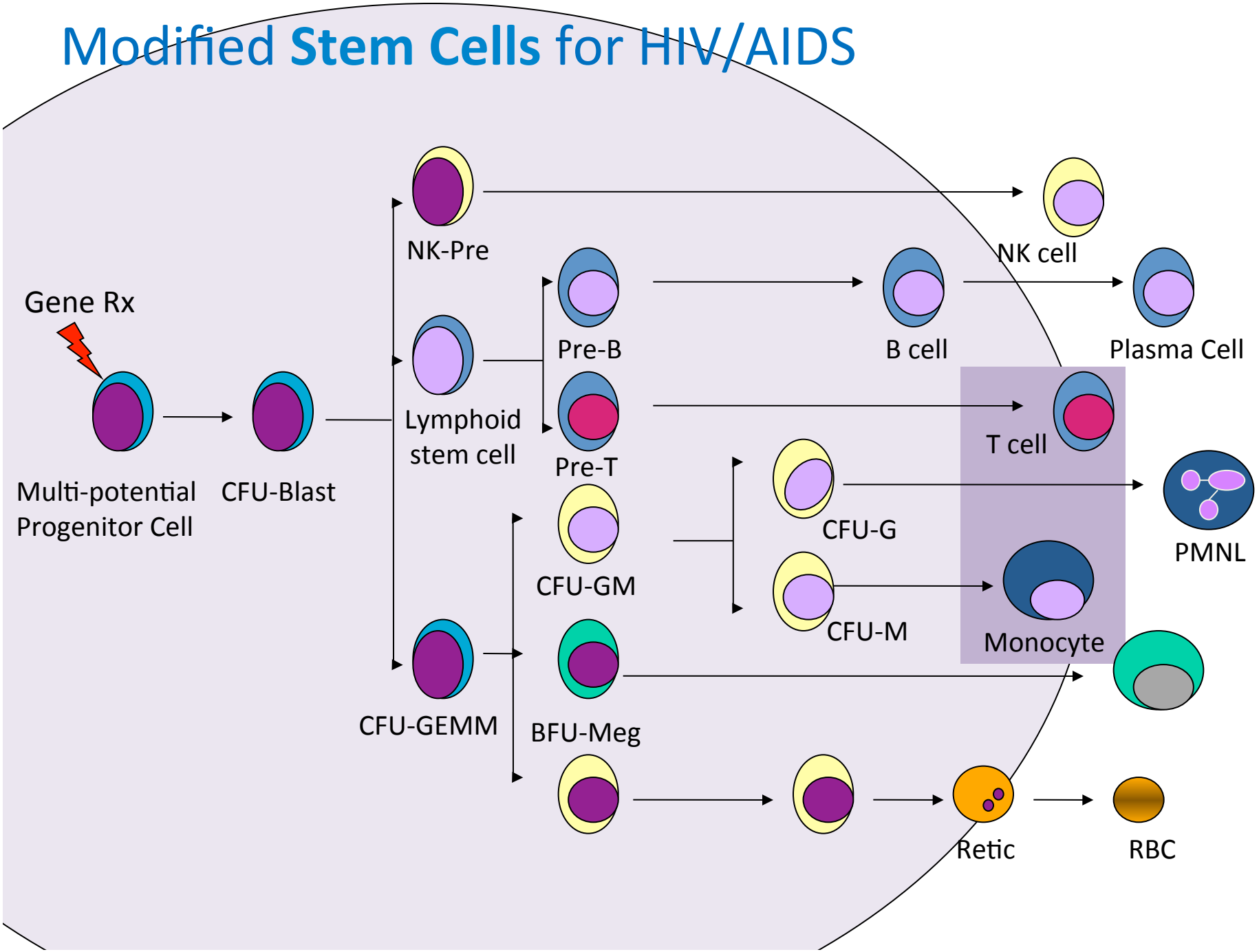
HIV/AIDS Stem Cell-Based Therapy

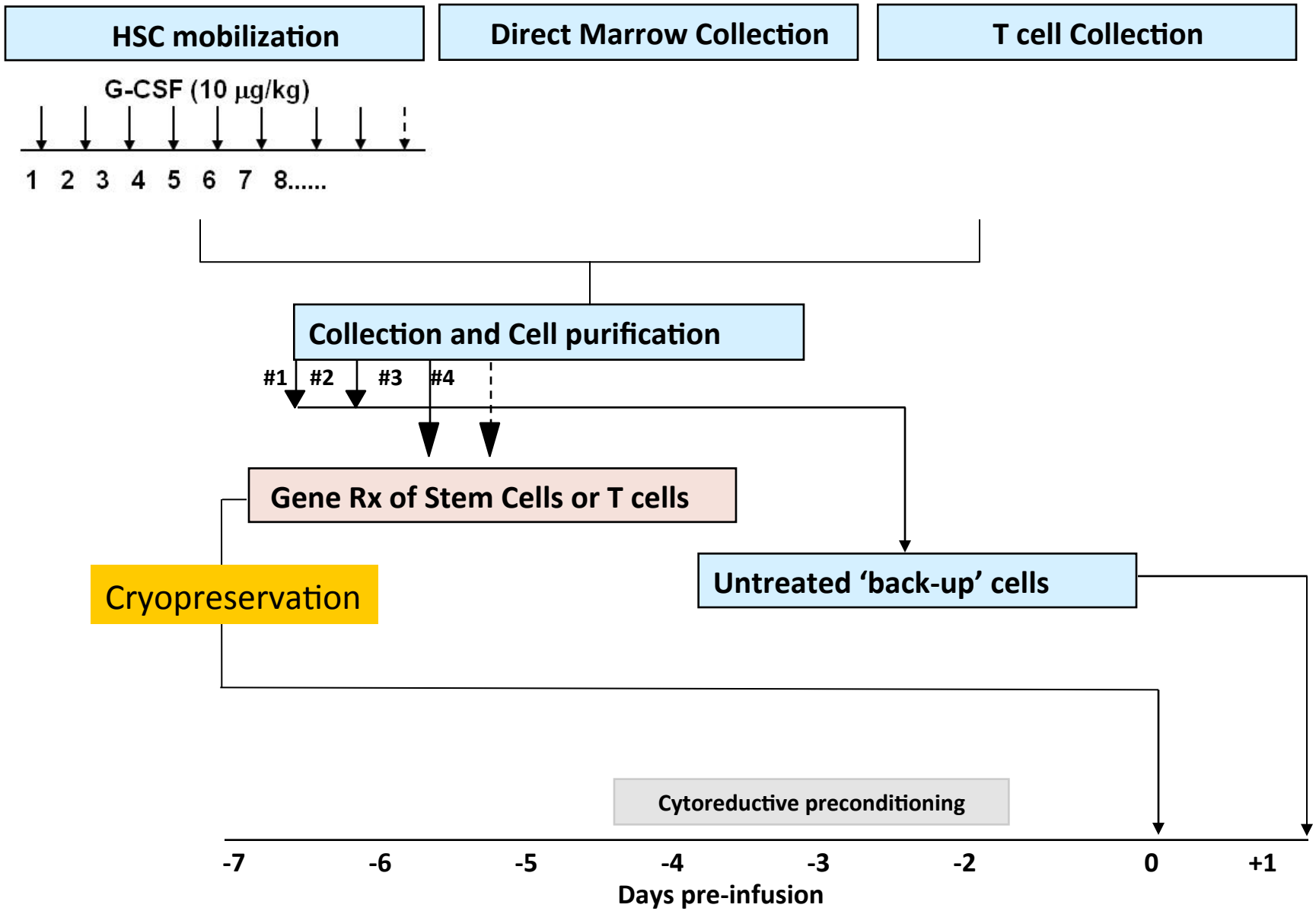
How do we best design the studies that take this to the clinic?



Modified **Stem Cells** for HIV/AIDS



Cell Collection & Processing



Challenges to Study Design

- Success of standard of care antiretroviral therapy [ARV]
- Choice of optimal population for first-in-human therapy
- Choice of endpoint: surrogate markers for antiviral effect, safety of ARV interruption, optimal latency measurements
- Optimal regimen for use of cytoreductive therapy in a non-cancer setting
- Choice of autologous vs allogeneic stem cell product

Initiating Antiretroviral Therapy in Treatment-Naive Patients

(Last updated March 29, 2012; last reviewed March 27, 2012)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count:
  - CD4 count <350 cells/mm^3 **(AI)**
  - CD4 count 350 to 500 cells/mm^3 **(AII)**
  - CD4 count >500 cells/mm^3 **(BIII)**
- Regardless of CD4 count, initiation of ART is strongly recommended for individuals with the following conditions:
  - Pregnancy **(AI)** (see perinatal guidelines for more detailed discussion)
  - History of an AIDS-defining illness **(AI)**
  - HIV-associated nephropathy (HIVAN) **(AII)**
  - HIV/hepatitis B virus (HBV) coinfection **(AII)**
- Effective ART also has been shown to prevent transmission of HIV from an infected individual to a sexual partner; therefore, ART should be offered to patients who are at risk of transmitting HIV to sexual partners (**AI** [heterosexuals] or **AIII** [other transmission risk groups]; see text for discussion).
- Patients starting ART should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence **(AIII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion*

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Success of standard of care antiretroviral therapy [ART]

- ART has become more convenient to take, less toxic, fewer [7%] virologic non-responders
- Little commercial interest in a cellular alternative to anti-HIV chemotherapy; more interest in supportive therapy which competes for patients
- DHHS Guidelines recommend early start of ARV in most patients*
- Concern: Continued HIV infection in nearly all patients
  Pathogenetic mechanisms remain active on ART
  Short and long term toxicity
  Cost
  Long-term effects of early treatment still unknown

* http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Choice of optimal population for first-in-human therapy

- Determined by the question of the study: safety, feasibility, effectiveness

- Determined by the risk of the method
  - T cell infusion vs stem cell transplant
  - Allogeneic vs autologous cell infusion

- Determined by the ultimate goal of therapy

Choice of endpoint

- Surrogate markers for antiviral effect
- Safety of ART interruption
- Optimal latency measurements

Optimal regimen for use of cytoreductive therapy in a non-cancer setting: unresolved questions

- Choice of autologous vs allogeneic cell product

- What is the optimal cytoreductive therapy for induction of endogenous homeostatic growth & engraftment factors?
  e.g. cyclophosphamide pre-T cell infusion; busulfan pre-HSCT

- What is the necessary ablative vs non-ablative regimen for engraftment of stem cells?

- Do we learn essential answers to these questions in cancer patients or do we have to address them in healthy HIV/AIDS patients?