Danger from the Wild: HIV, Can We Conquer It?

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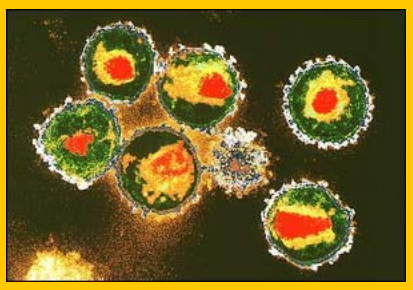
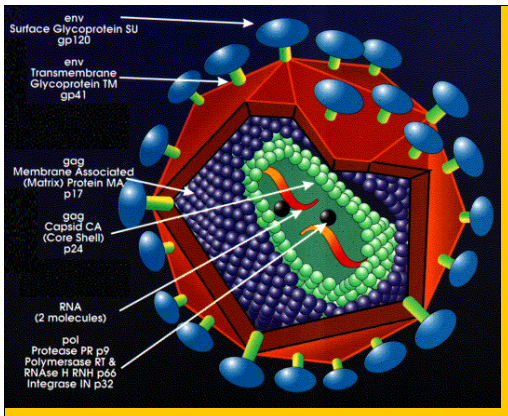




Part III

The Grand Challenge: Engineering Immunity

Reprogramming the Immune System using Gene Therapy

- What is needed is a vaccine or therapy that brings into play antibodies or other anti-viral proteins
- Vectors could be used to bring genes encoding such proteins into the immune system

Reprogramming the Immune System using Gene Therapy

- Such an approach liberates us to use modern protein design methods to create antibody-like proteins that can be programmed into the immune system.
- The vectors will be put into stem cells which should then develop into the cells that make antibody, B cells.

Overall Goal for the Project

To direct blood stem cells to develop into B cells capable of making therapeutic molecules against HIV and other pathogens.

General Approach

- The immune system is remarkable but not perfect
  - Repertoire of antibodies is large but not infinite, there are holes
  - Even if repertoire includes a particular antibody, we may not be able to elicit the response with a available antigen

General Approach

- So we have as a goal to engineer immune cells to do new, valuable things, such as making antibodies or T cells or intracellular immunogens like RNAi
- This is the Engineering Immunity project

Specific Approaches

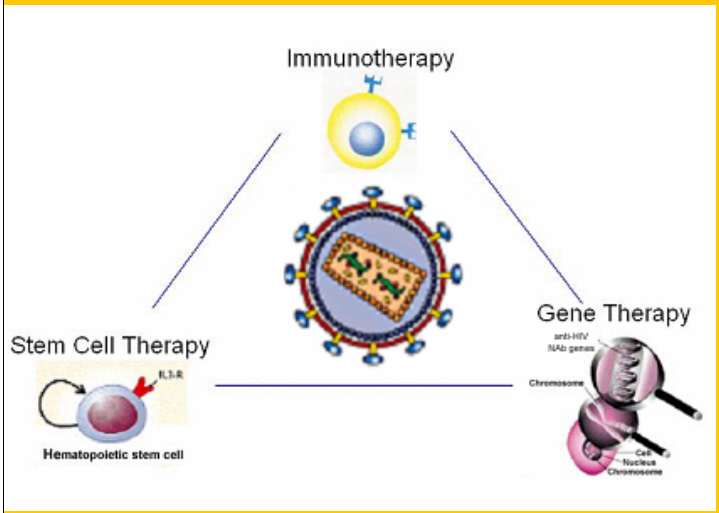
Have taken 3 specific approaches:

- Intracellular immunization using RNAi
  - Mainly directed against HIV
- Engineering T cells to react with tumor antigens (almost in Phase I trial)
- Engineering B cells to make prespecified monoclonal antibodies or antibody-like proteins, targeting HIV

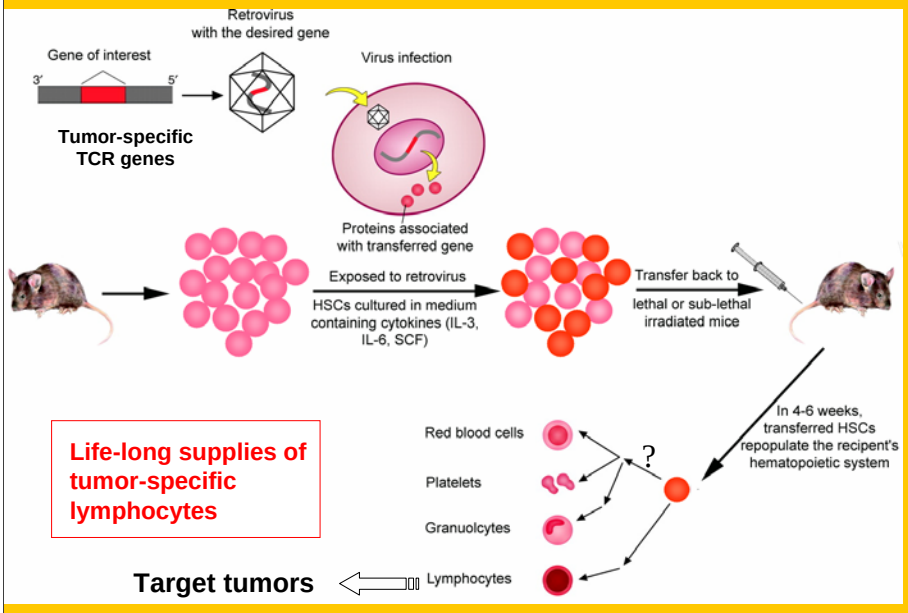
General Methodology

- All three have a common methodology: to use retrovirus vectors to program particular abilities into hematopoietic stem cells that give rise to B cells and T cells
- Thus, this is a gene therapy approach to stem cell modification

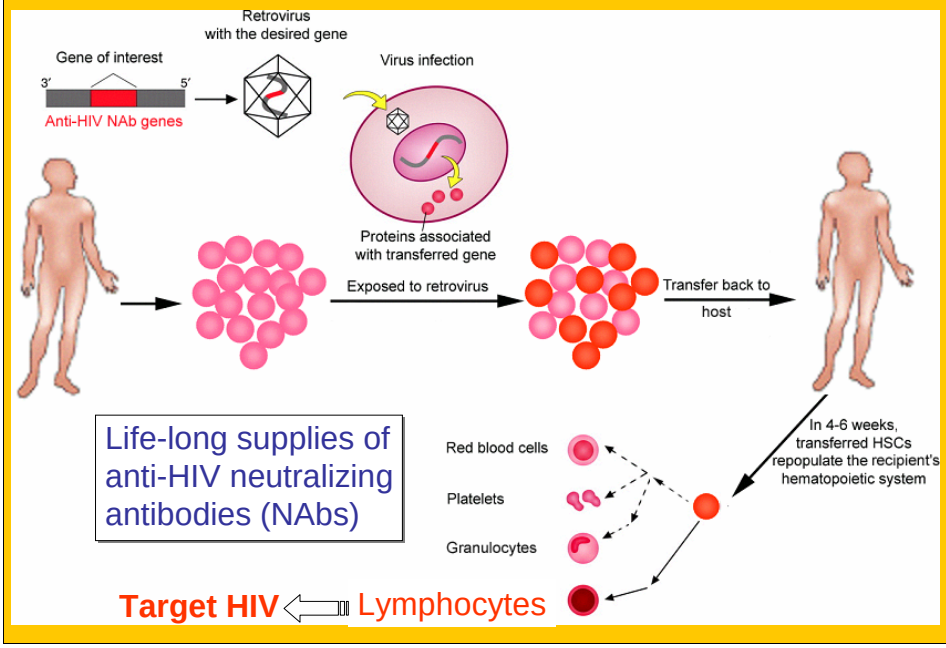
"Instructive Immunotherapy"



Program T Cells for Anti-tumor Immunity



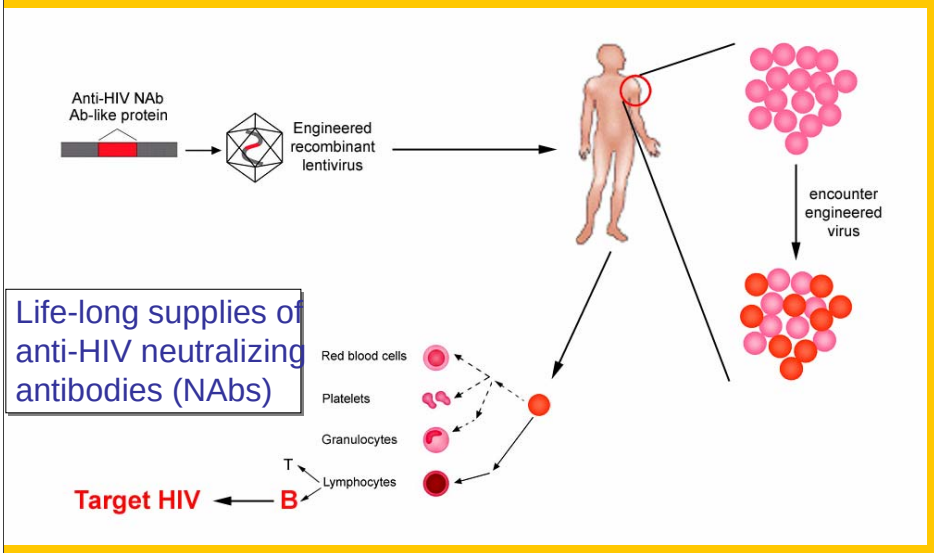
Our General Strategy for Modifying B cells:

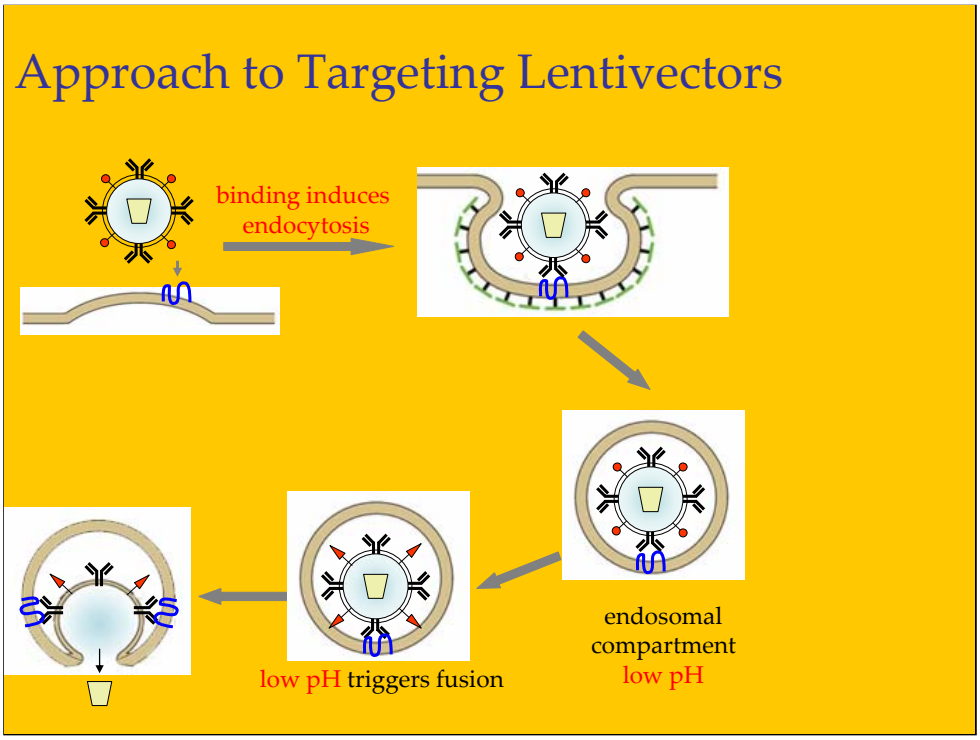


Life-long supplies of anti-HIV neutralizing antibodies (NAbs)

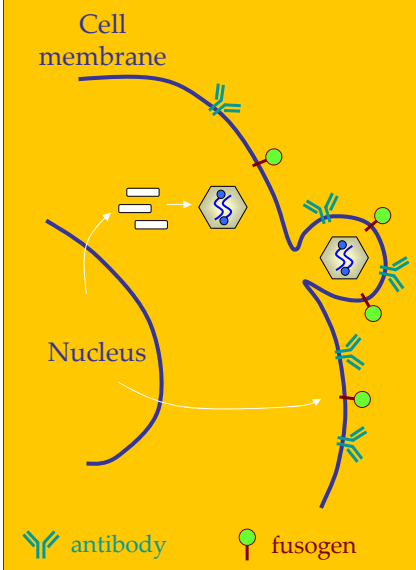
Target HIV ⇦

Overview of the Project




Approach to Targeting Lentivectors
binding induces endocytosis
endosomal compartment
low pH
low pH triggers fusion

Generation of Lentivector Envelope with Antibody and Fusogen



Co-transfection Plasmids

Lentiviral vector (FUGW)

Packaging plasmids (gag, pol)

Antibody gene plasmids (αCD20)

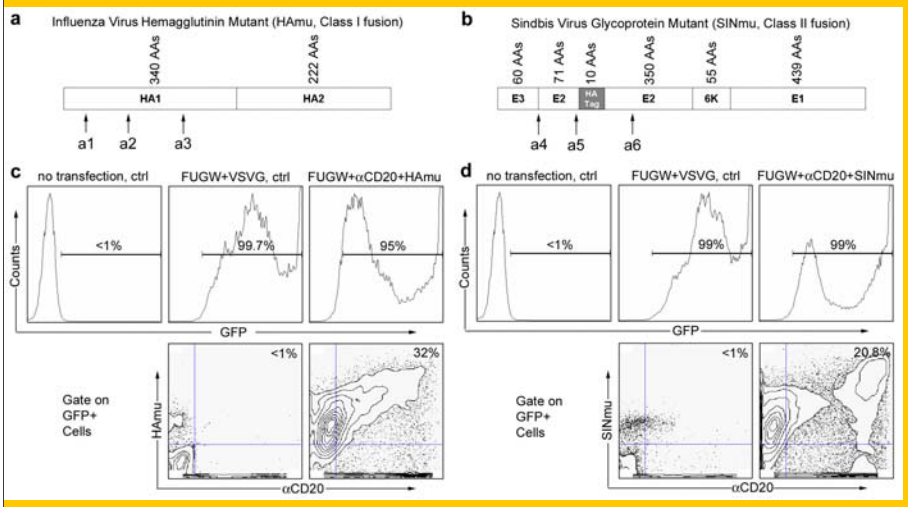
Antibody accessory proteins plasmids (Igα, Igβ)

Fusogen (HAmu or SINmu)

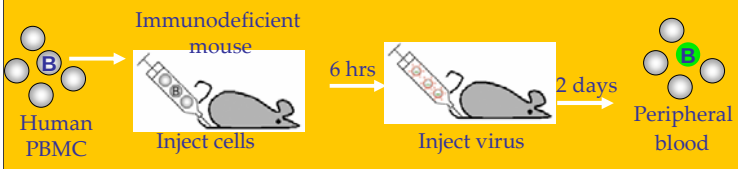
Co-display of Antibody and Fusogen on the Surface of 293T Packaging Cell Line

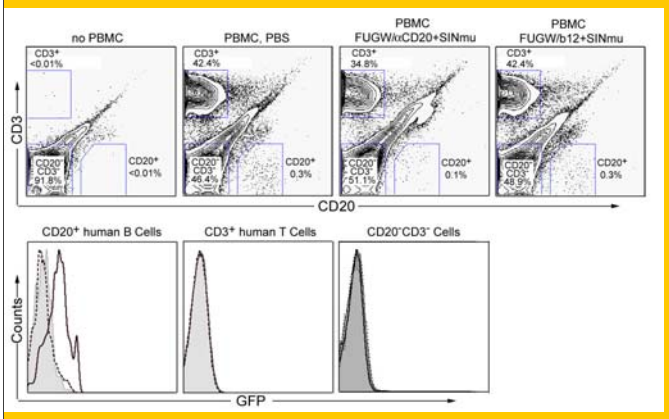
Class I fusogen

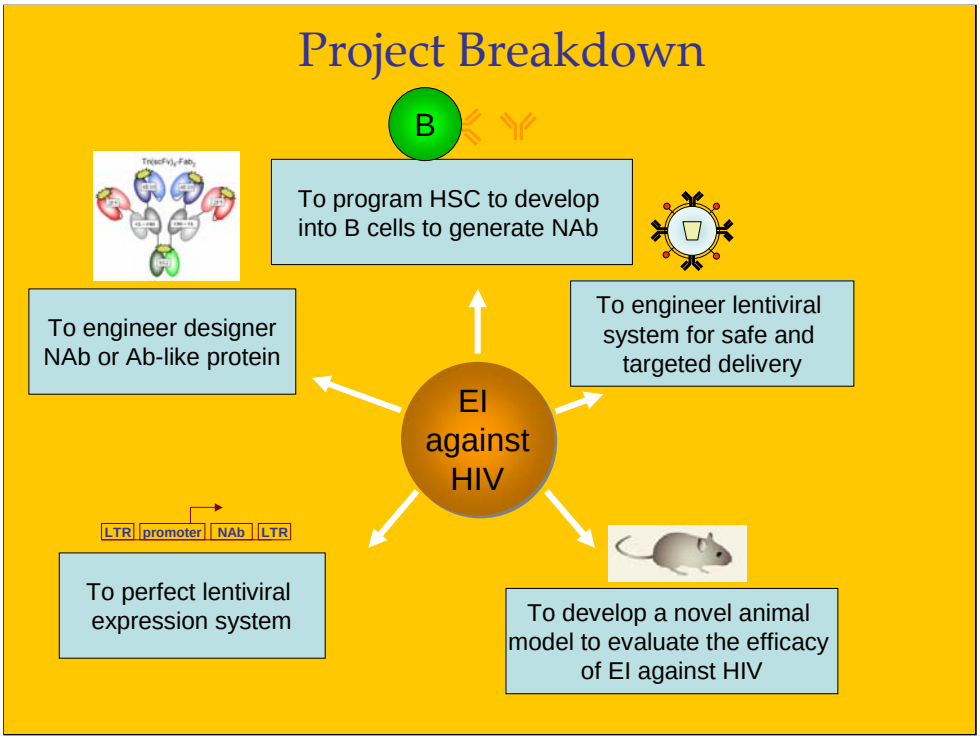
Class II fusogen



Targeting Primary Human B Cells *in vivo*






Project Breakdown
B
To program HSC to develop into B cells to generate NAb
To engineer designer NAb or Ab-like protein
To engineer lentiviral system for safe and targeted delivery
EI against HIV
LTR
promoter
NAb
LTR
To perfect lentiviral expression system
To develop a novel animal model to evaluate the efficacy of EI against HIV

To Take This to Humans

- Requires making blood stem cell transplant a routine, safe and reasonably-priced therapeutic intervention or developing targeted gene delivery in vivo
- Requires showing that gene therapy is generally safe and there have been doubts because of cancer in 3 out of 11 children treated for XSCID
  - Could design in safety features or use lentivirus (HIV)-based vectors

To Take This to Humans

- Requires much logistic work to get antibody secretion
- Potential benefits are enormous: cancer, HIV, other infectious diseases

Therapy → Vaccine

- So far, we conceive of a therapy as the end result of the engineering immunity initiative
- However, with vectors targeted to blood stem cells in living animals, a vaccine becomes a possible goal
- In any case, my overall message is: no harm in thinking big when thinking small has been so uniformly problematic

Acknowledgements

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