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How Close Are We To A Gene Therapy Cure of HIV?

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Kirby Institute

Contents

- Treatment Vs. Cure/Remission

What Is In Store for HIV for Treatment?

What Cures Are Being Proposed?

- Gene Therapy Out Of The Limelight

Has Gene Therapy Had Its Chance?

What Have We Learnt From Past and Existing Gene Therapies?

- Delivering Gene Therapy

Enhancing The Efficacy Of Gene Therapy Regimens

Driving Down The Cost Of Facilitating Gene Therapy

Treatment Vs. Cure/Remission – Treatment/Prophylaxis Options

- 1987 – Antiretroviral Monotherapy
- 1996 – Antiretroviral Combinational Therapy
- 2004 – Single-Tablet Combinational Therapy
- 2012 – PrEP
- 2016 – U=U (Undetectable = Untransmissible)

- Future – Long-Acting Interventions

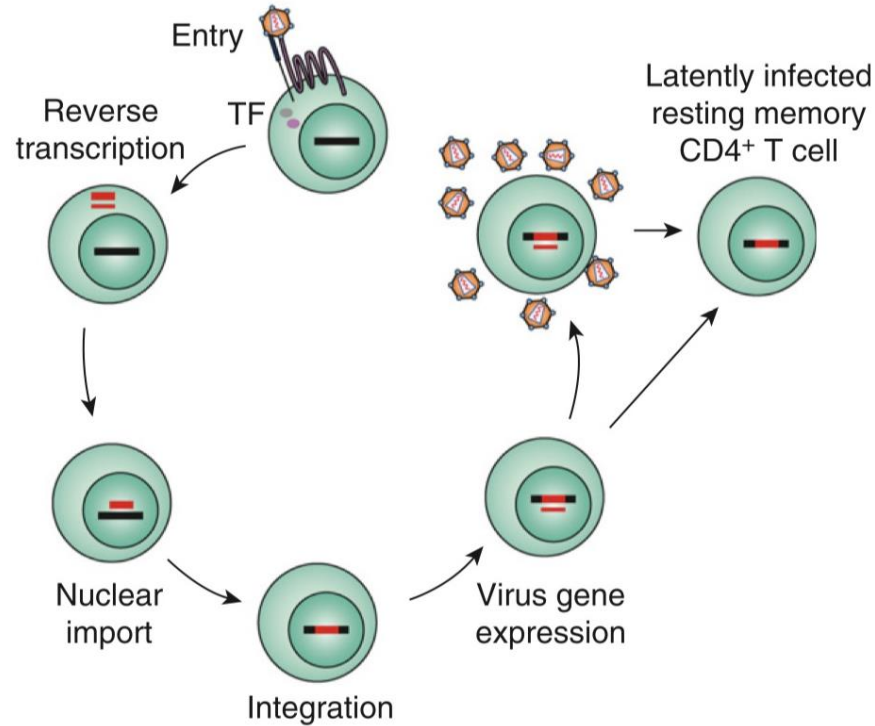
Treatment Vs. Cure/Remission – Do We Need A Cure?

- Alternative to ART
 - Salvage Therapy
 - Drug-Resistant Infections
- Convenience/Compliance
 - Removal From Need of Periodic ART Dosing
- De-stigmatization

Treatment Vs. Cure/Remission – What's In A Cure?

- Remission
 - Less Certainty, Although More Realistic?
 - Cure
 - More Certainty, Greater Impact
 - Sterilizing Cures
 - Complete removal of all traces of virus from person
 - Functional Cures
 - Incomplete removal of virus, but protects from AIDS and spread
- Aim: Safe Removal From Medication (With NO Repercussions)

Treatment Vs. Cure/Remission – HIV Latent Reservoir



Treatment Vs. Cure/Remission – How Do We Achieve A Cure?

- A Cure Must Target The Latent Reservoir
- Exhaustive Avenues To Cure

Treatment Vs. Cure/Remission – Exhibit A: Stem Cell Transplantation

- Complete Overhaul of Host Immune System
 - Provision of Immune System From Donor Deficient in CCR5 ($\Delta\Delta 32\text{CCR5}$)
 - CCR5 is an important attachment factor required for HIV infection
- It Works
 - Second “Berlin Patient” Cured This Way
 - Limited Success in Replication
- It Doesn’t Work
 - Requires Whole Body Irradiation & Chemotherapeutic Conditioning
 - Need To Find Compatible Donor To Limit GVHD

Treatment Vs. Cure/Remission – Exhibit B: Therapeutic Vaccines

- Vaccinate To Teach Immune System How To Recognize Infected Cells (Perhaps Latently Infected Cells Too)
 - Delayed Rebound in SIV Model (Poxvirus Vector)
 - Recent RIVER Study Showed No Therapeutic Effect
 - Newer Antigen-Loaded Dendritic Cells (Proof of Concept)
- Experiencing a ‘Second Wave’ of Support

Treatment Vs. Cure/Remission – Exhibit C: Latency Reversing Agents

- What Are We?
 - Small Molecules That Disrupt Cellular Latency
 - Antibodies and Cytokines
 - Histone Deacetylase Inhibitors
 - Protein Kinase C Agonists
 - H3K9 Histone Methyltransferase Inhibitors
- How Does This Target The Reservoir?
 - ‘Wakes Up’ Cells (Including Infected Cells)

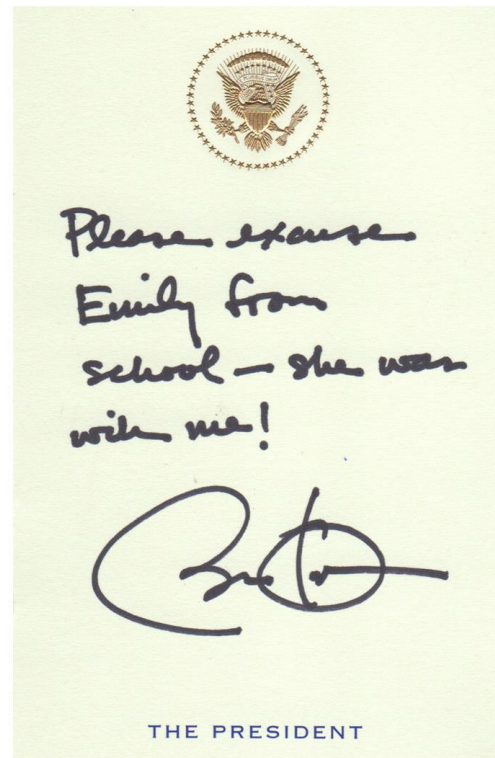
Treatment Vs. Cure/Remission – Exhibit C: Latency Reversing Agents

- Kick and Kill Strategy
 - Kill Provided By:
 - Cytotoxic T Cells (Naturally or Artificially Developed)
 - Recombinant Antibodies
 - Time
- Evidence of Efficacy?
 - > 6 Clinical Trials (PI/II)
 - Limited Reduction in Reservoir Size
 - Limited Activation In Vivo
 - Potentially Risky?

Treatment Vs. Cure/Remission – Exhibit D: Gene Therapy

- Use Of Novel Or Synthetic Genes To Produce Therapy
- Requires Delivery Of Genes To Cells
 - Typically By Heavily Attenuated Viruses, including HIV
- Gene Therapy Aims To Be Permanent
 - Results In Genetic Modification Of The Host





Treatment Vs. Cure/Remission – Exhibit D: Gene Therapy

- Genetic Modification of Cells To:
 - Control Spread
 - Protect new cells from acquiring virus
 - Enforce Latency
 - Prevent infected cells from spreading virus
 - Active Clearance
 - Use adaptive killing to erode the latent reservoir

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Driving Down The Cost Of Facilitating Gene Therapy

Gene Therapy Out Of The Limelight – The Present

- 2006 – First Licensed (For Cancer) Worldwide (China)
- 2012 – First Licensed (For Lipoprotein Lipase Deficiency) in EU
- 2017 – First Licensed (For Cancer) In USA
- 2017 – Second Licensed (For Cancer) In USA
- 2018 – Second Licensed (For Cancer) In EU
- Deployment and Commercial Readiness
 - \$100s of Millions In Manufacturing Infrastructure
 - Safety Profile Understood
- Industry Invigorated By Gene Therapy Potential

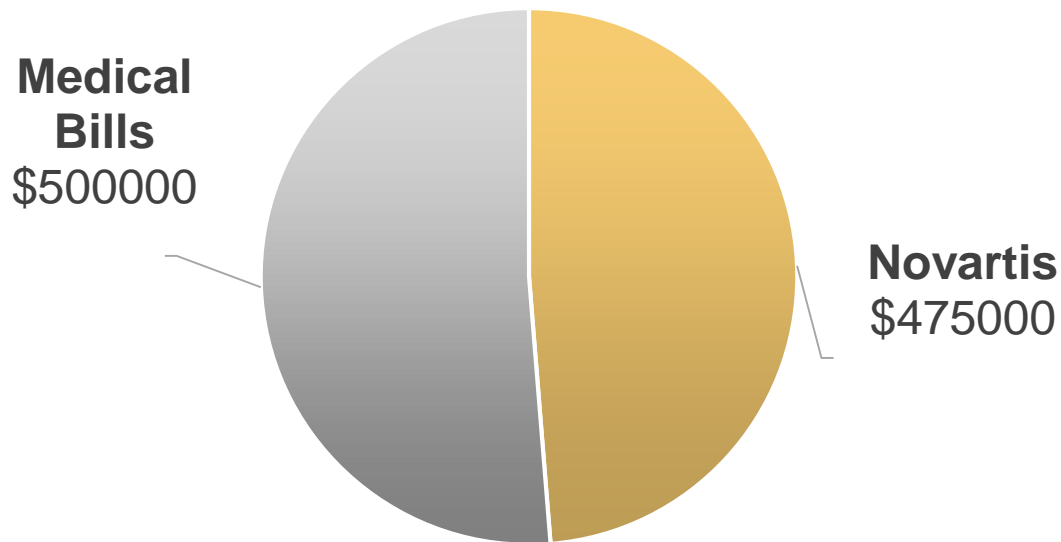
Gene Therapy Out Of The Limelight – The Past

- Conceptualized as Early as 1990
 - Earliest Clinical Trial in 1998
 - Dozens of Clinical Trials Since
 - >6 Clinical Trials Listed on [ClinicalTrials.org](https://clinicaltrials.org) In-Progress/Recruitment
- Phase I Trials Results Show Good Safety
- Phase II Trials Results Show Poor Efficacy

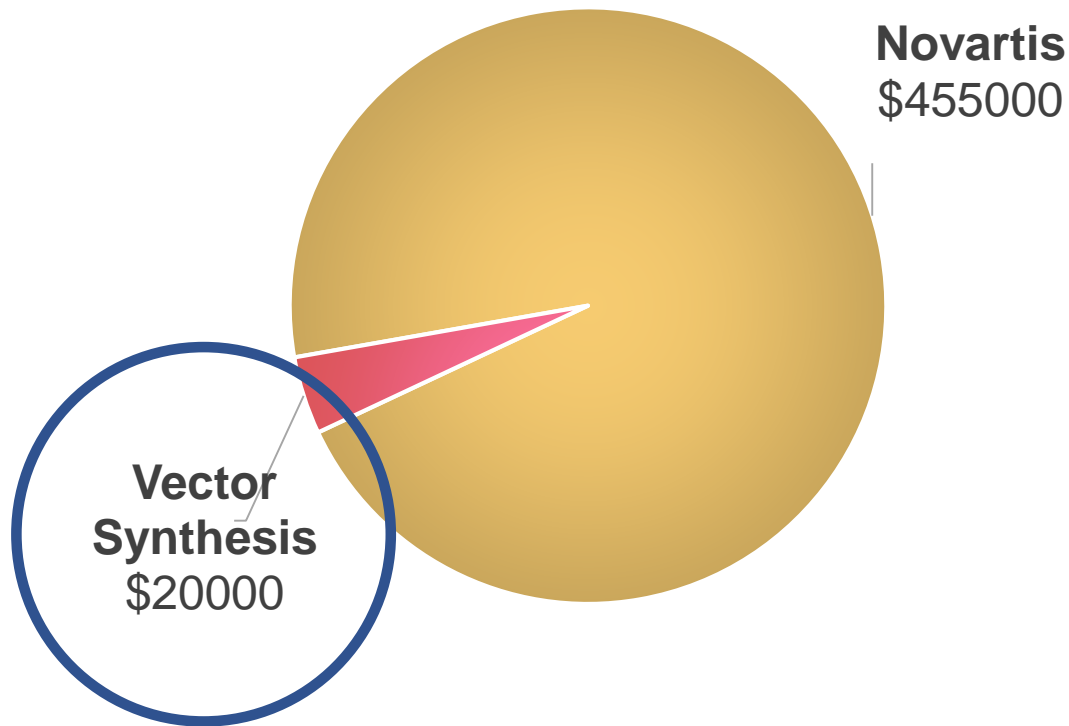
Gene Therapy Out Of The Limelight – Economics of Therapy

- Expensive; Outrageously Expensive
 - “Million Dollar Cures”
- Feasibly Accessible By The Masses?

Gene Therapy Out Of The Limelight – Economics of Therapy (Kymriah Model)



Gene Therapy Out Of The Limelight – Economics of Therapy (Kymriah Model)



Gene Therapy Out Of The Limelight – Economics of Therapy

- Expensive; Outrageously Expensive
 - “Million Dollar Cures”
- Feasibly Accessible By The Masses?
- How Can We Make It More Affordable?

Gene Therapy Out Of The Limelight – The Future

- Need To Address Efficacy Problem
 - Shortcoming of Phase II Trials Show Rapid Loss Of Protection
 - Related to loss of genetically modified cells
- Cheap...
 - ...Enough For The First World?
 - ...Enough For Developing Nations?

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Delivering Gene Therapy – Shortcomings Of Previous Attempts

- Efficacy
 - Poor Engraftment Of Transfused Product
 - Low Long-Term Viability Of Transfused Product
- Why?
 - Methodology To Confer Genetic Modification Is Suboptimal

Delivering Gene Therapy – Current Modus Operandi

1. Harvest T Cells (Via Leukapheresis)
2. Activate T Cells
 - Increases Number Of Genetically Modifiable Cells
 - Increases Compatibility Of Viral Vector System With Cells
3. Transduce T Cells (Using Viral Vector)
4. Further Expansion of T cells
5. Reinfusion
6. Continued Monitoring

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Delivering Gene Therapy – Genetic Modification Of Activated T Cells

- Activation Causes Cellular Exhaustion
 - Loss Of Long-Term Functional Activity
 - Poor Engraftment
 - Lowered Proliferative Potential
- Activation Of Bulk T Cells Elicits Unintended Effects
 - Is The Activation Of T Cells Incapable Of An Antiviral Response Necessary?

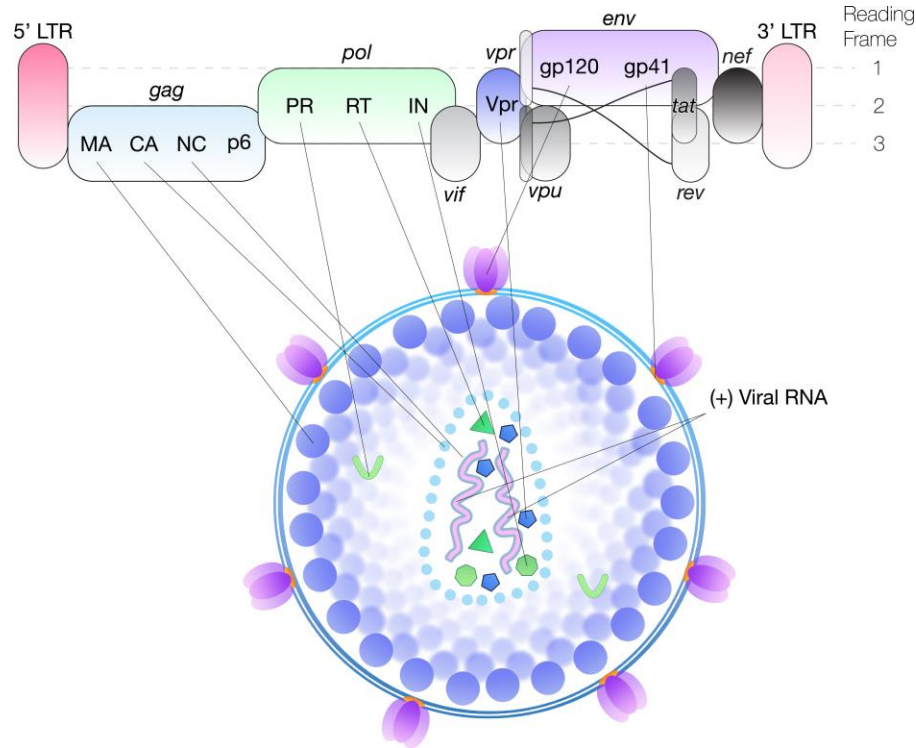
Delivering Gene Therapy – Genetic Modification Of Activated T Cells

- Why Are Groups Pre-Activating T Cells?
 - T Cells Emerge With Immediate Effector Function
 - Great for anti-cancer capabilities
 - Increases Compatibility With Existing Viral Vector Systems
 - Major bottleneck in gene therapy

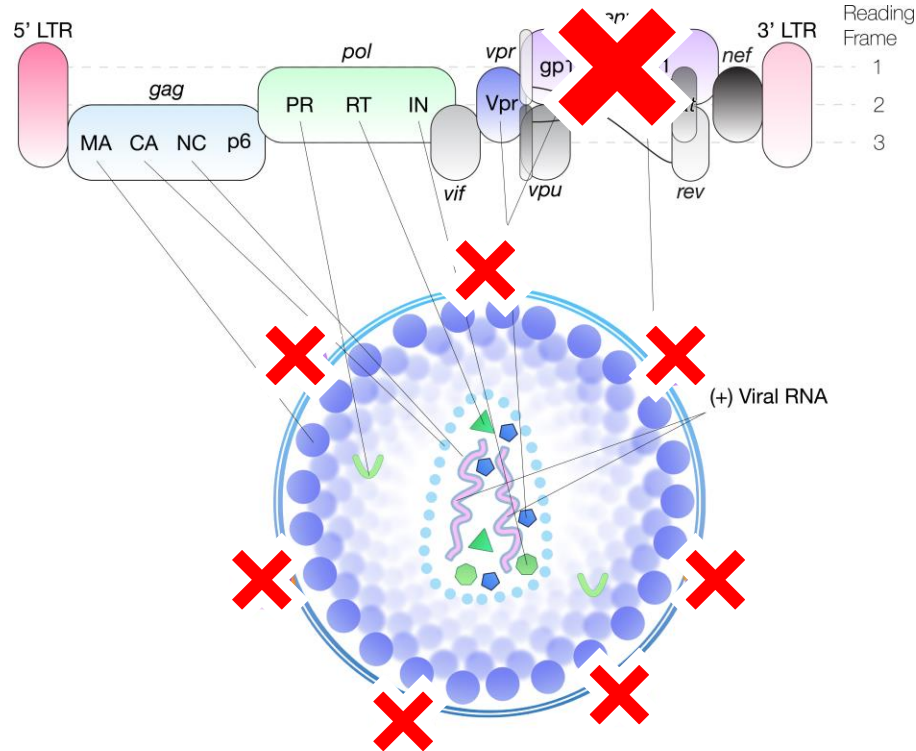
Delivering Gene Therapy – Genetic Modification Of Activated T Cells



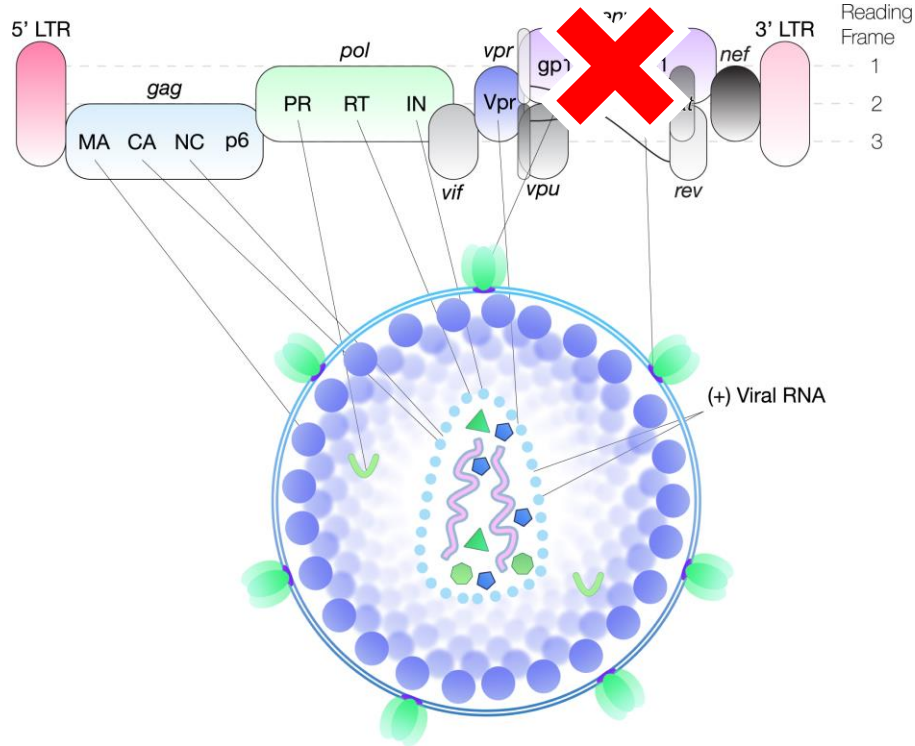
Delivering Gene Therapy – Current Tools



Delivering Gene Therapy – Current Tools



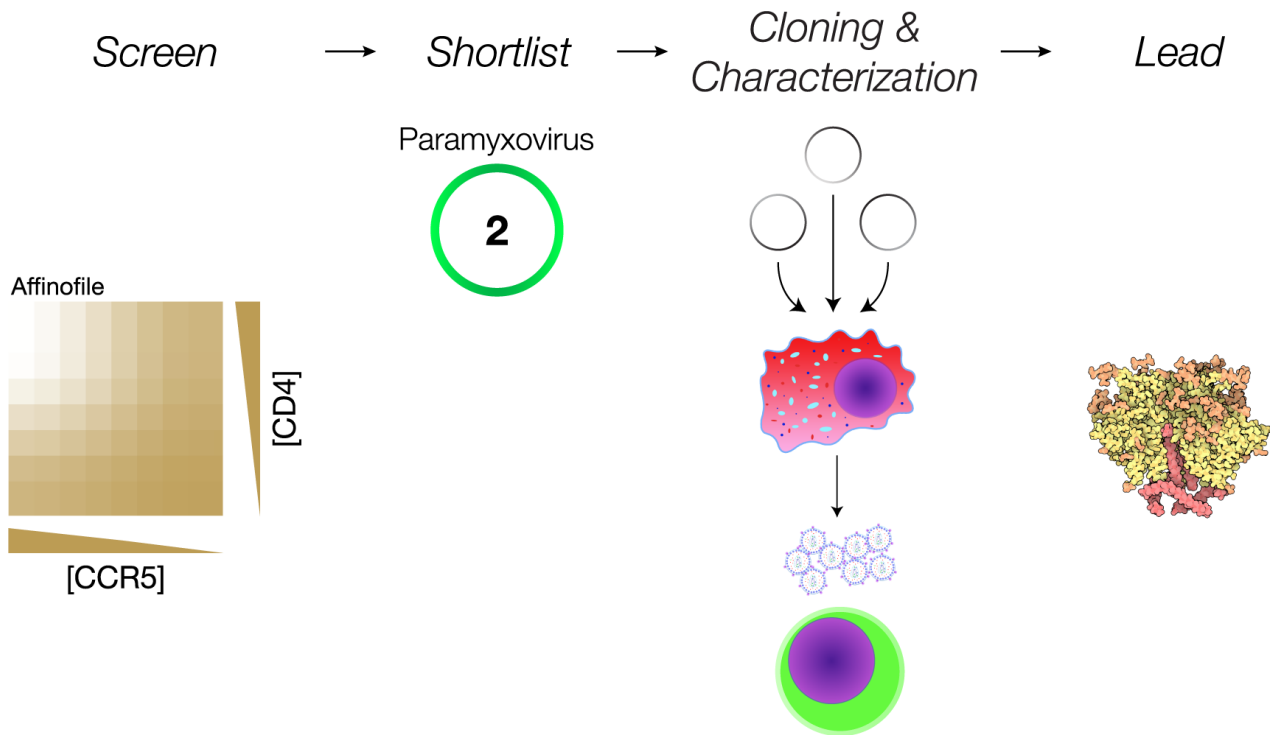
Delivering Gene Therapy – Current Tools



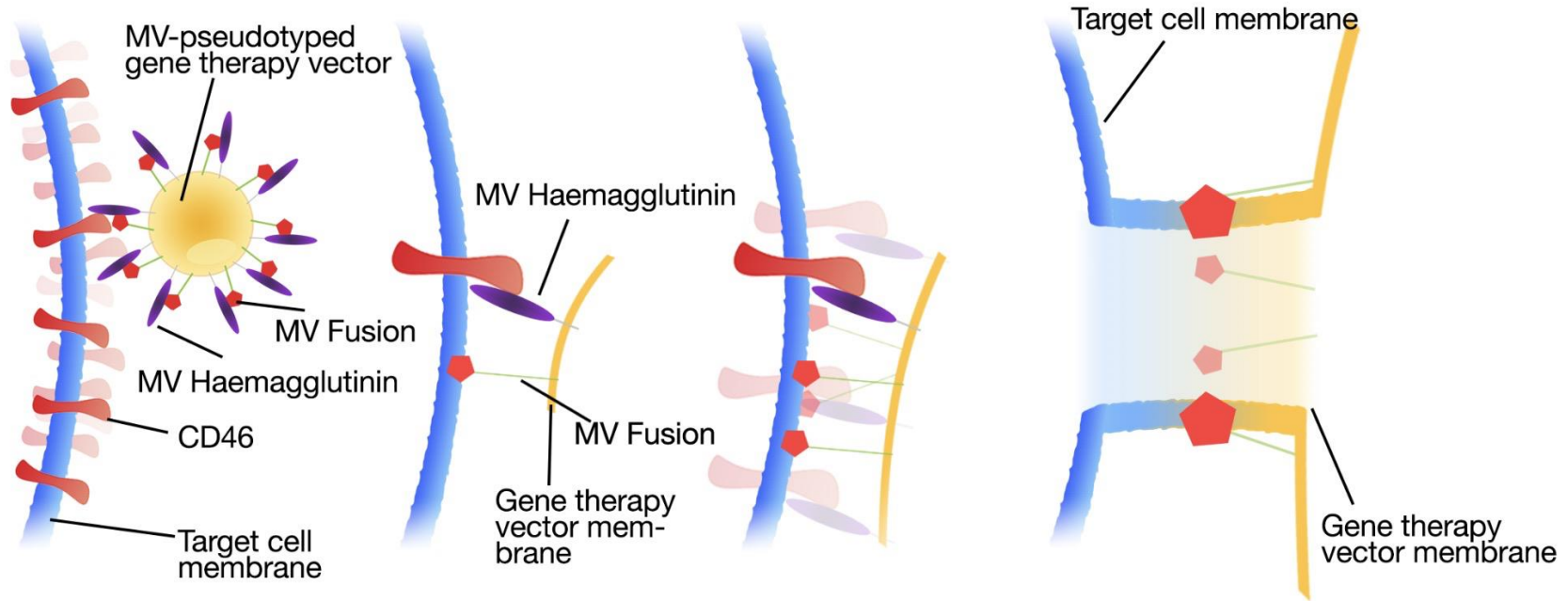
Delivering Gene Therapy – Current Tools

- Broadly-Reaching Envelope
 - Viral Envelope From Vesicular Stomatitis Virus
 - Not Compatible With Resting T Cells
- Need New Envelope
- Viral Reprogramming
 - To Increase Safety And Efficacy
- Coalesce Select Plasmids To Increase Production Efficiency

Delivering Gene Therapy – New Tools

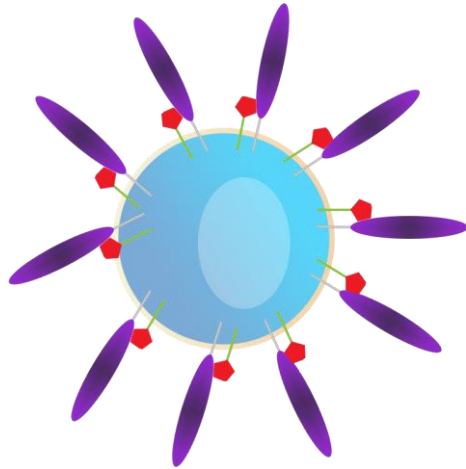


Targeting Resting T Lymphocytes – New Tools – Measles

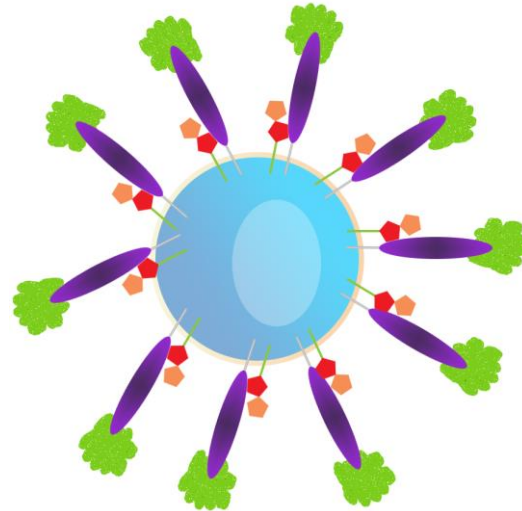


Targeting Resting T Lymphocytes – New Tools – Measles

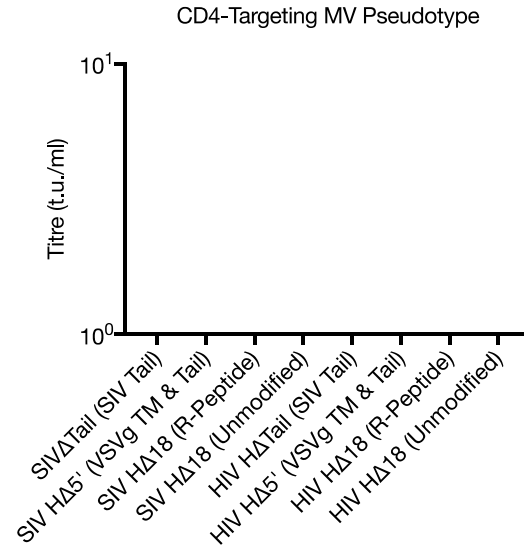
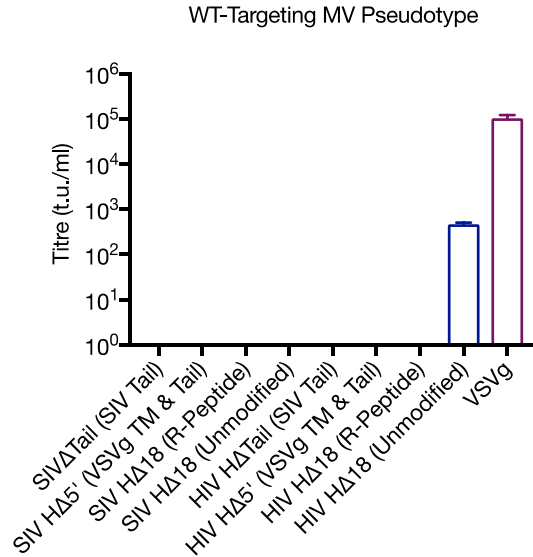
Wild-Type
Epithelial Cells
Immune Cells



Re-Targeted
T Cells

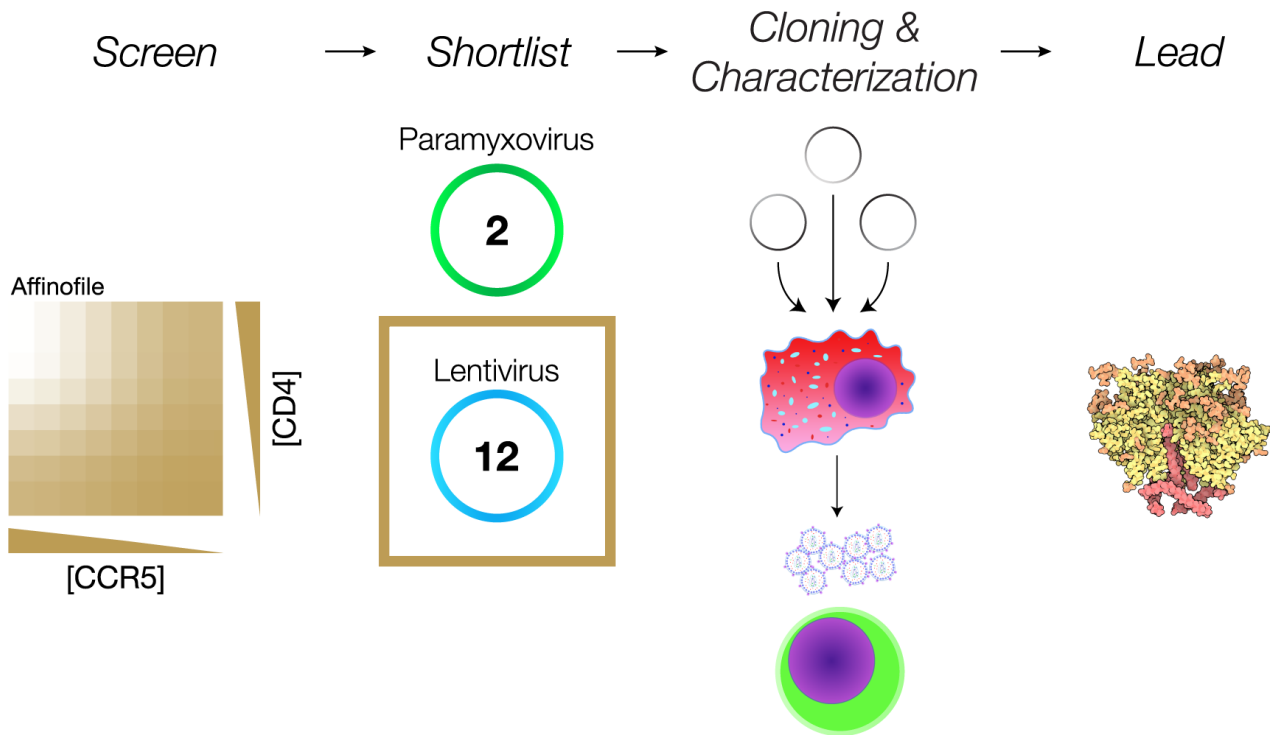


Targeting Resting T Lymphocytes – New Tools – Measles

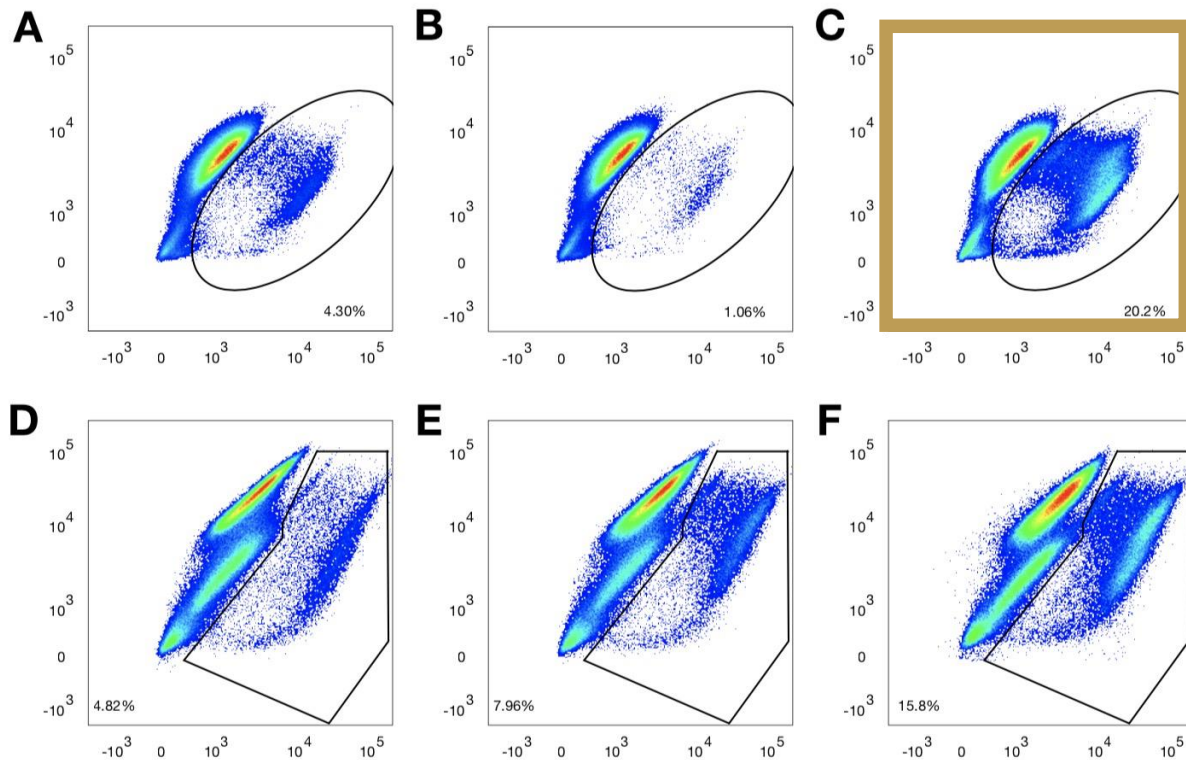


– Are There Any Envelopes With Natural Affinity For CD4⁺ Cells?

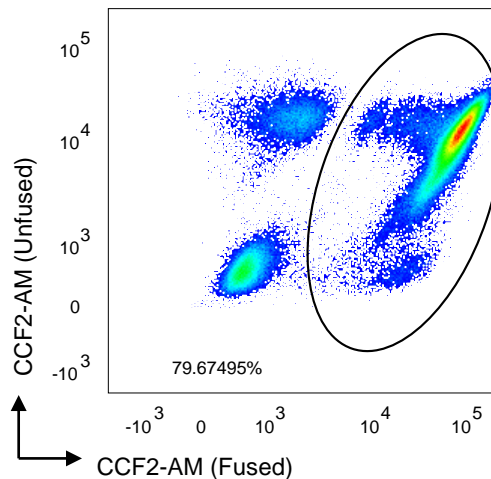
Delivering Gene Therapy – New Tools



Delivering Gene Therapy – Selecting A Better Pseudotype – HIV-1



Delivering Gene Therapy – Selecting A Better Pseudotype – HIV-1



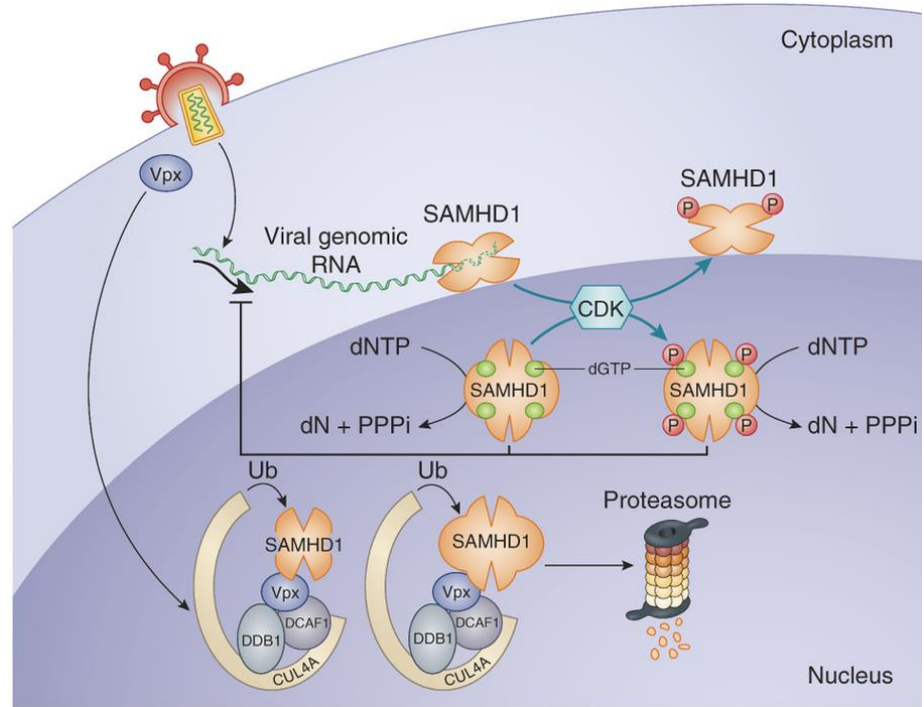
Population	Fusion (%)
Whole CD4 ⁺	95.2
Central Memory	98.1
Effector Memory	96.7
Naïve	95.6
Terminally Differentiated	55.0

Delivering Gene Therapy – Selecting A Lead Pseudotype – HIV-1

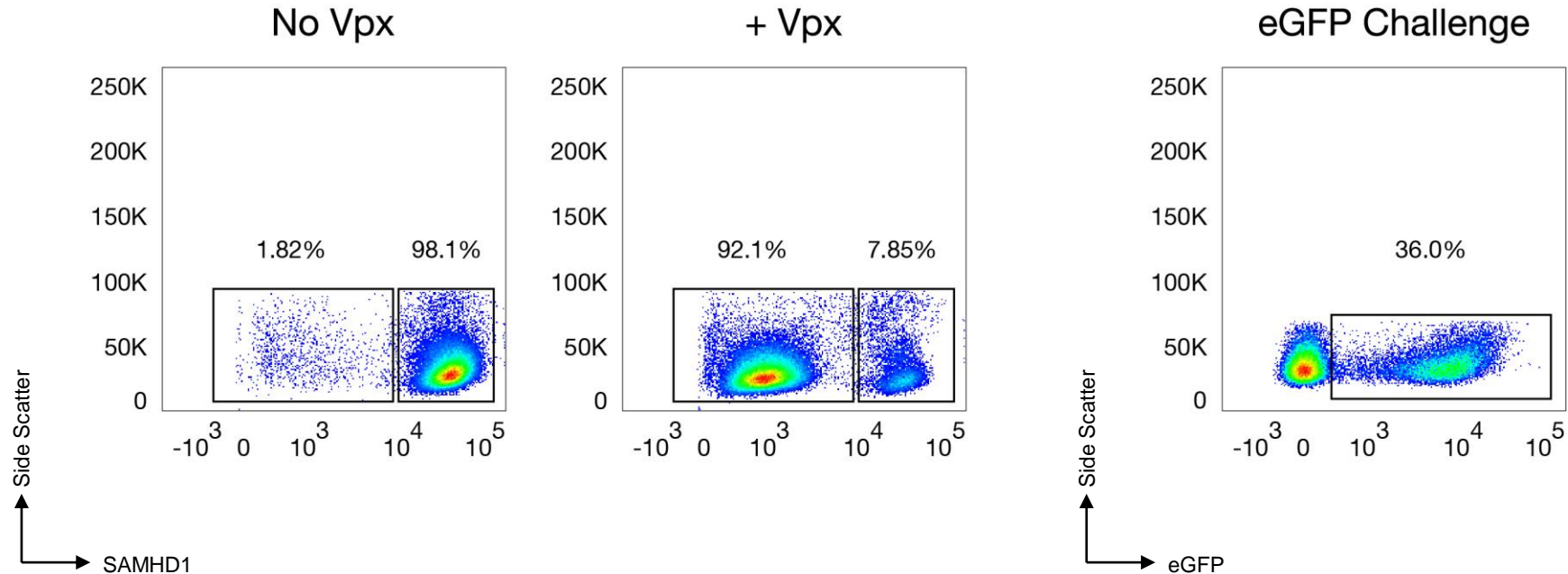
- HIV-1 Envelopes Resolve Restriction At The Plasma Membrane
 - Natural Compatibility With Resting T Cells
 - Works Synergistically With Lentiviral Components
- Lentiviral Particle Delivery \neq Genetic Modification
 - Efficient Cytoplasmic Delivery Is A Breakthrough
 - Does Not Resolve Restrictions At The Nuclear Membrane

Delivering Gene Therapy – Restrictions At The Nuclear Membrane

- SAMHD1 Acts As A Restriction Factor
 - Interferes With Viral Function
- Antagonized By Vpx
 - Encoded By HIV-2 And Some SIV



Delivering Gene Therapy – Vpx Delivery Enhances Transduction



Delivering Gene Therapy – Vpx Implications On HIV Cure

- Need To Address Efficacy Problem
 - Shortcoming of Phase II Trials Show Rapid Loss Of Protection
 - Related to loss of genetically modified cells
- Cheap...
 - ...Enough For The First World?
 - ...Enough For Developing Nations?

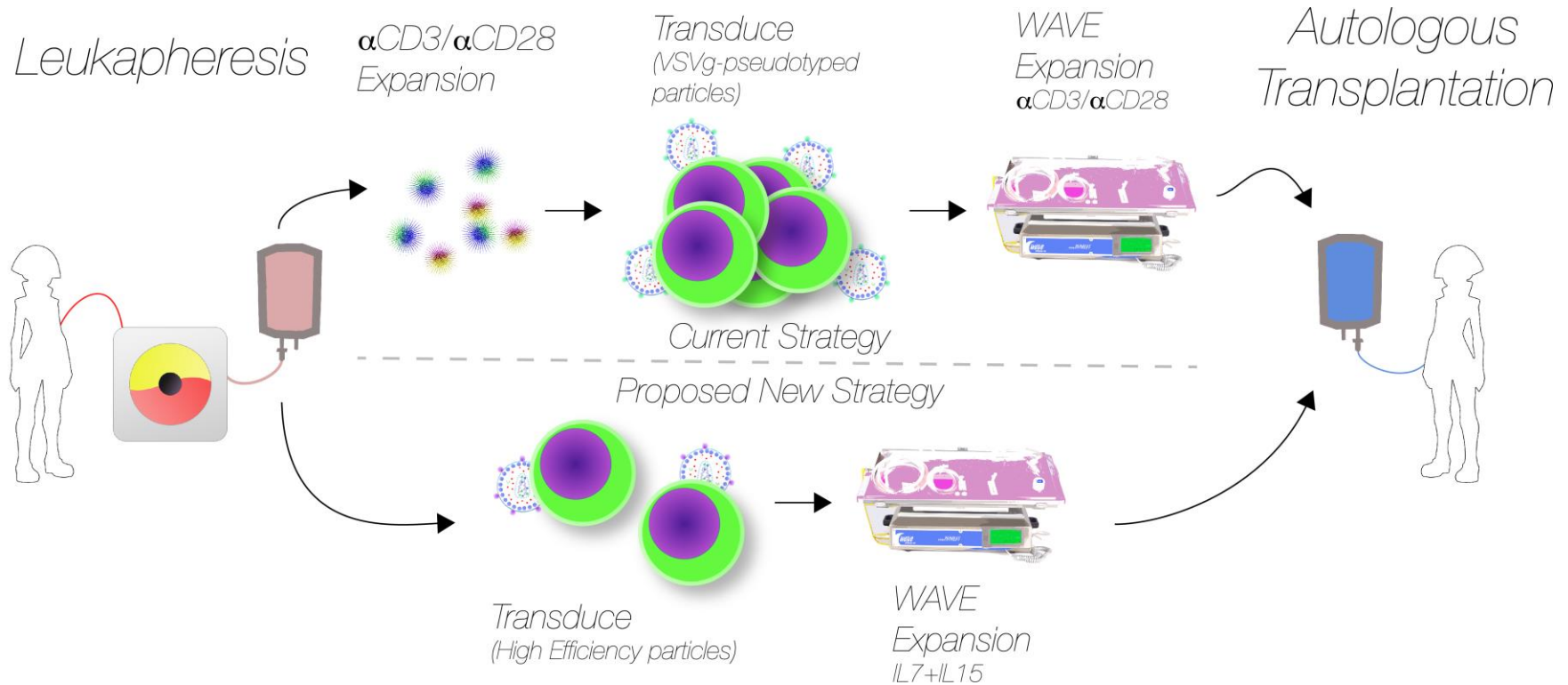
Delivering Gene Therapy – Vpx Implications On HIV Cure

- ~~Need To Address Efficacy Problem~~
 - ~~Shortcoming of Phase II Trials Show Rapid Loss Of Protection~~
 - ~~Related to loss of genetically modified cells~~
- Genetic Modification Of Resting T Cells Breathes Optimism Into HIV Cure
- Cheap...
 - ...Enough For The First World?
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Delivering Gene Therapy – Vpx Implications On HIV Cure

- ~~• Need To Address Efficacy Problem~~
 - ~~• Shortcoming of Phase II Trials Show Rapid Loss Of Protection~~
 - ~~• Related to loss of genetically modified cells~~
- ~~– Genetic Modification Of Resting T Cells Breathes Optimism Into HIV Cure~~
- ~~• Cheap...~~
 - ~~• ...Enough For The First World?~~
 - ~~• ...Enough For Developing Nations?~~
- Vpx Decreases Amount Of Vector Required To Genetically Modify Cells By 2-3 Orders Of Magnitude

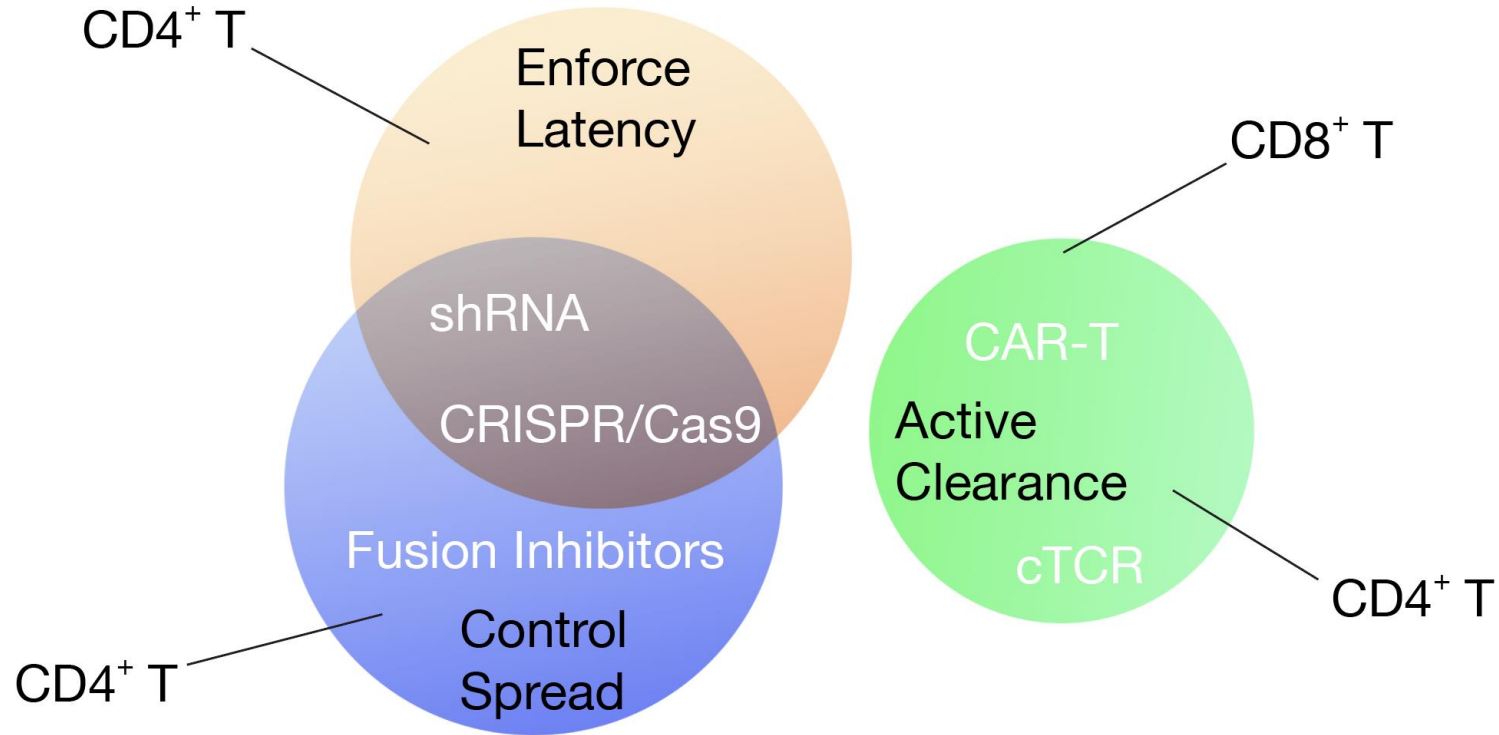
Delivering Gene Therapy – A New Gene Modification Model



Delivering Gene Therapy – Aspirations For A Gene Therapy HIV Cure

- Genetic Modification of Cells To:
 - Control Spread
 - Protect new cells from acquiring virus
 - Enforce Latency
 - Prevent infected cells from spreading virus
 - Active Clearance
 - Use adaptive killing to erode the latent reservoir

Delivering Gene Therapy – Aspirations For A Gene Therapy HIV Cure



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