Design and Development Considerations for Immune Augmentation To Assist in Virus Eradication

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Challenges To Effective Anti-viral HIV Immunotherapy Development

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- Inter- and intra-patient mutational diversity
- Functionality in the compromised immune environment of an infected patient
- Generation durable cytotoxic memory T cell responses
- Ability to decrease plasma viral load
- Ability to reduce integrated viral reservoir

Case Study: AGS-004 Developed To Address These Challenges

AGS-004 is a completely autologous RNA-loaded Dendritic Cell-based immunotherapy

- Antigen source: RNA encoding Gag, Nef, Rev, and Vpr amplified from the subjects own infectious plasma

- Antigen vehicle: PME-CD40L Dendritic cells*
  - Matured by sequential exposure to general inflammatory cytokine (IFN-γ) followed by an adaptive signal (CD40L)

**Post-Maturation Electroporation of DCs with HIV antigen RNA + CD40L RNA*

Inter-patient Viral Diversity Must Be Addressed

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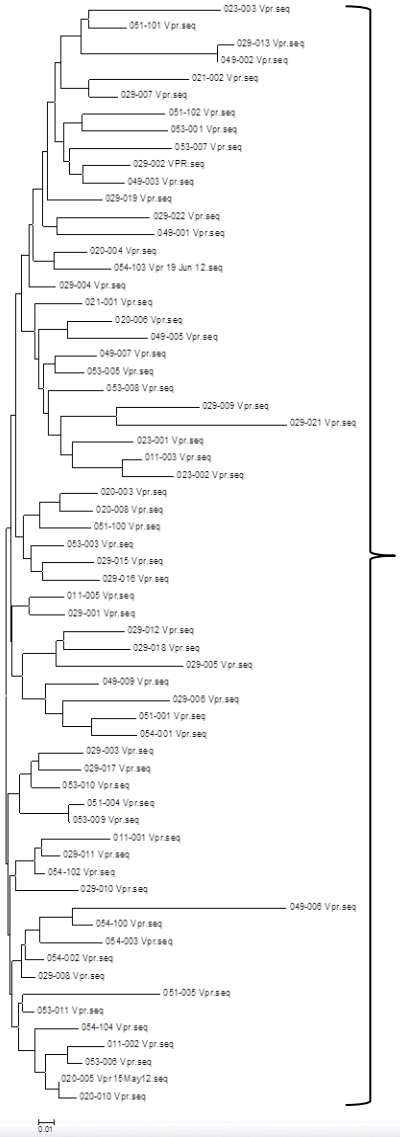
- Consensus antigen approaches have sub-optimal population coverage due to virus antigen sequence diversity
- Effective anti-virus immunization must address antigenic patient-to-patient epitope diversity
- AGS-004 RNA antigen payload is perfectly matched to each patient's viral antigens (Gag, Vpr, Nef, Rev)



Phylogenetic tree of VPR sequences of patients treated with AGS-004

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Intra-patient Viral Diversity Demands An Autologous Approach

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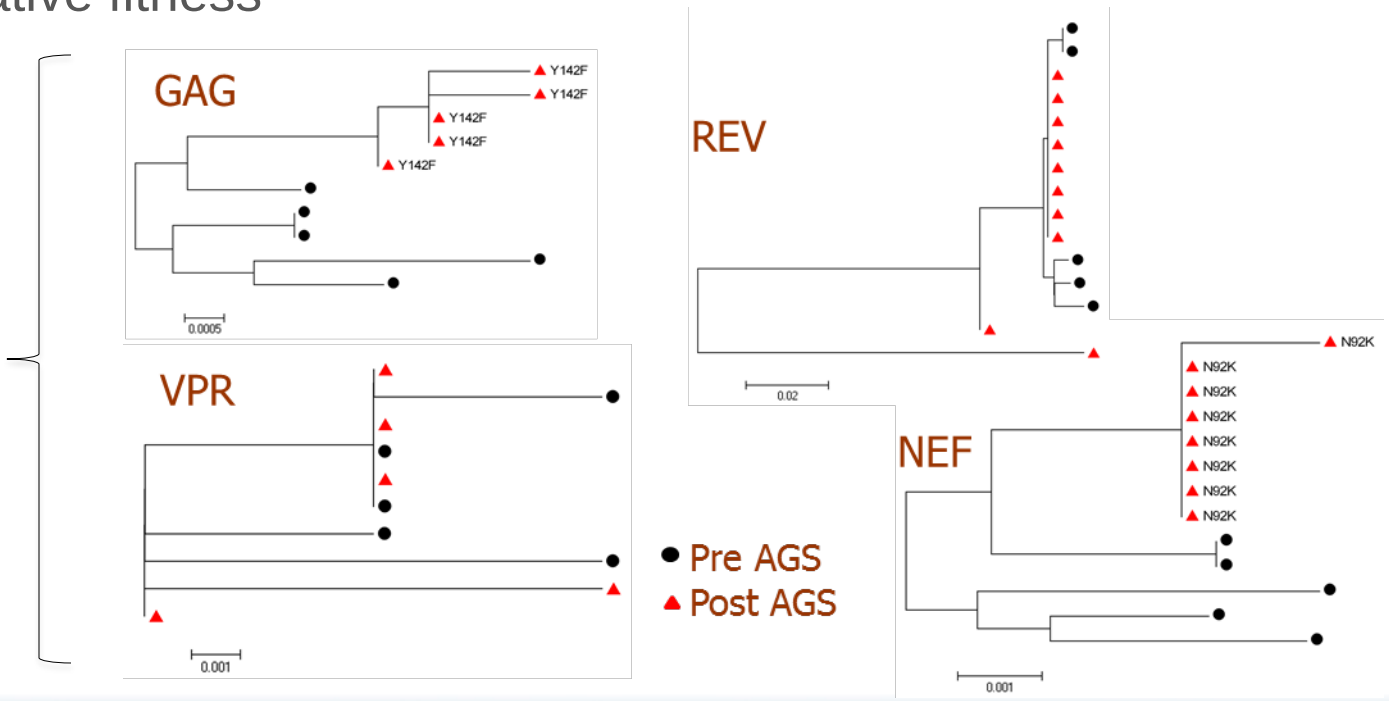
- Large virus sequence diversity exists within each infected patient
- Predicts poor outcome for strategies using consensus antigens
- AGS-004 RNA antigen payload captures the patient-specific quasi-species of Gag, Vpr, Nef and Rev
- AGS-004 decreases virus diversity and forces the virus into a state of poor replicative fitness

Phylogenetic tree analysis of HIV antigen sequences pre- and post-AGS-004 treatment



Effective Immunotherapies Should Limit Reliance On Normal Immune Function *In vivo*

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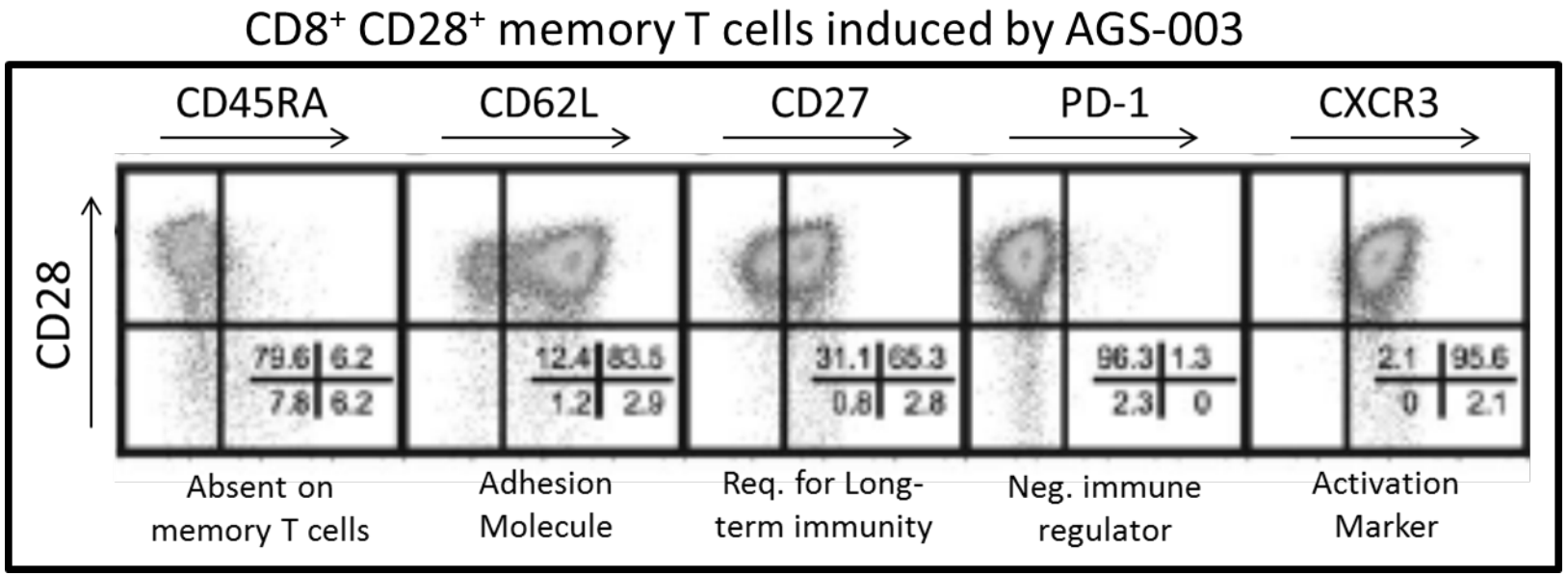
- CD4+ T cell help and APCs are impaired in HIV-infected patients
- Durable immunity requires central and effector memory T cell responses
- AGS-004 generates $CD8^+CD28^+CD45RA^-PD\text{-}1^-$ memory T cells (*see below*)
- AGS-004 has no requirement for CD4+ T cell help (due to co-electroporation of RNA encoding CD40L)
- AGS-004 DCs are resistant to HIV Vpr-induced IL-12 blockade



Ability To Decrease Plasma Viral Load Should Be Demonstrated

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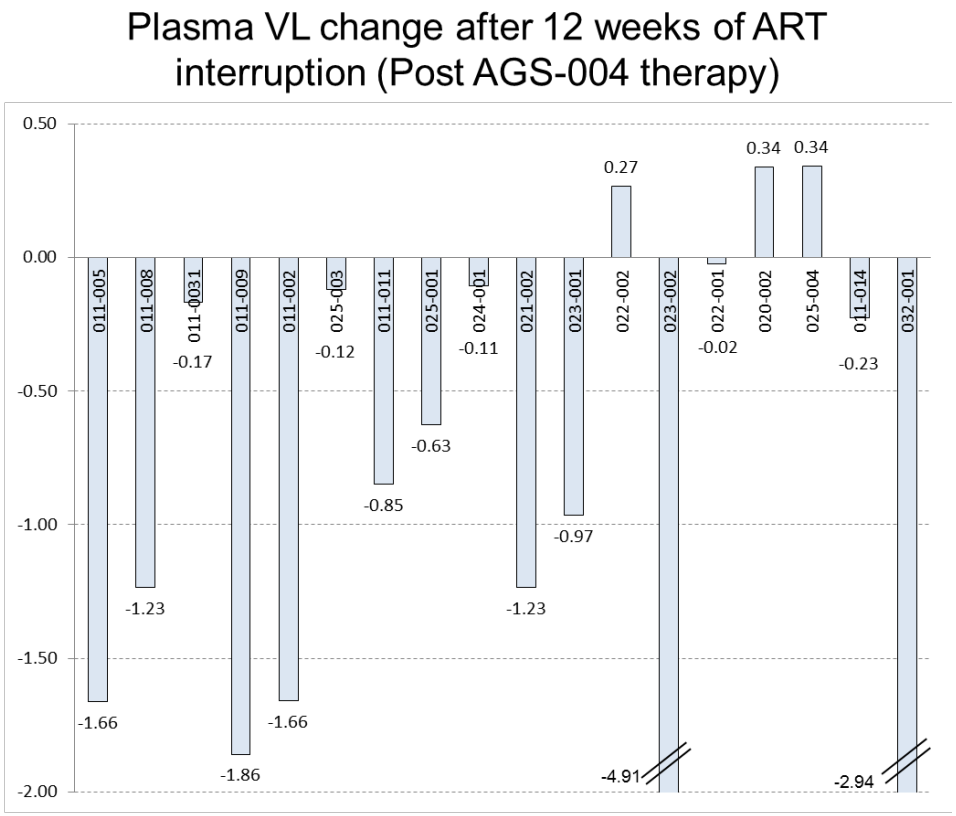
- Six monthly doses of AGS-004 shown to reduce viral load set point in the majority of chronically infected patients (compared to pre-ART set point)

SID	Pre-ART set point	VL after 12 week ART drug stop	Change
011-005	4.909463	3.246352	-1.66311
011-008	5.371753	4.138231	-1.23352
011-003	4.059684	3.890429	-0.16926
011-009	4.398899	2.539808	-1.85909
011-002	5.402898	3.743935	-1.65896
025-003	5.69897	5.580656	-0.11831
011-011	4.175664	3.327987	-0.84768
025-001	5.69897	5.073056	-0.62591
024-002	4.999812	5.111761	0.111949
024-001	4.195172	4.089779	-0.10539
021-002	5.862699	4.62907	-1.23363
023-001	5.385175	4.420125	-0.96505
022-002	4.103324	4.36977	0.266447
023-002	4.905275	1.722335	-4.90528
020-001	5.215976	5.419273	0.203298
022-001	4.620142	4.597462	-0.02268
020-002	5.328495	5.665	0.336505
025-004	4.279993	4.62	0.340007
011-014	5.375325	5.15	-0.22533
032-001	5.69897	2.755	-2.94397



In this clinical study, 16 of 24 patients had a mean reduction in VL of 1.2Log

Ability To Decrease Latent Viral Reservoir Should Be Demonstrated

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- ~25% of 19 evaluable patients treated with AGS-004 had a significant reduction in integrated viral DNA in circulating CD4+ T cells

	Mean # HIV genomes/10^6 $CD4^+$ T cells	
N	Pre-AGS-004	Post-AGS-004
15	7553	7633
4	4141	2894

- The decrease in the latent reservoir was associated with a longer delay in viral rebound during ART interruption, longer time to peak viral load and longer duration of ART interruption (years in some cases)

Conclusions

- Effective anti-viral immune augmentation combined with latent reservoir mobilization is a promising strategy for HIV eradication
- The immunotherapeutic component must address the unique challenges associated with HIV infection
- AGS-004 is a promising candidate for use in eradication strategies