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## Citation

Li, C, ZL Brumme, T Miura, PC Rosato, J Sela, CJ Brumme, D Heckerman, F Pereyra, BD Walker, and MA Brockman. 2009. P09-11. Reduced replication capacity of NL4-3 chimeric viruses encoding RT-Integrase sequences from HIV-1 elite controllers. *Retrovirology* 6(Suppl 3): P124.

## Published Version

doi://10.1186/1742-4690-6-S3-P124

## Permanent link

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## P09-11. Reduced replication capacity of NL4-3 chimeric viruses encoding RT-Integrase sequences from HIV-1 elite controllers

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from AIDS Vaccine 2009  
Paris, France. 19–22 October 2009

Published: 22 October 2009

Retrovirology 2009, 6(Suppl 3):P124 doi:10.1186/1742-4690-6-S3-P124

This abstract is available from: <http://www.retrovirology.com/content/6/S3/P124>

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### Background

Spontaneous control of HIV to <50 copies RNA/ml is observed in rare individuals. An improved understanding of this phenomenon may provide insight into host mechanisms that can be modulated for therapeutic benefit by vaccines. Recent studies of these 'elite' controllers (EC) revealed HLA-associated changes in Gag-Protease that resulted in reduced replication capacity. This project assessed the possibility of immune-mediated defects in the Pol gene (RT-Integrase) of EC.

### Methods

Chimeric NL4-3 mutants encoding patient plasma-derived RT-Integrase sequences from EC (N = 58) and chronic progressors (N = 50) were constructed by homologous recombination. Replication capacity (RC) for each variant strain was assessed using a GFP-reporter T cell assay. Results were correlated with clinical and host genetic factors, including CD4 count, plasma viral load (pVL), and patient HLA.

### Results

Viruses encoding Pol sequences from EC replicated significantly less well than those from individuals with progressive disease (Mann-Whitney,  $p < 0.0001$ ). No association was observed between RC and CD4 T cell count in EC or progressors, nor between RC and pVL in progressors (Spearman, all  $p > 0.05$ ). Viruses derived from HLA-B57+ EC (N = 20) appeared to replicate slower than those from

B57+ progressors (N = 8) ( $p = 0.004$ ). Similar results were observed between B51+ EC (N = 4) and B51+ progressors (N = 10) ( $p = 0.024$ ), but not between B27+ EC (N = 9) and B27+ progressors (N = 5) ( $p = 0.437$ ).

### Conclusion

This study extends previous observations for Gag and demonstrates that Pol variants from EC also display reduced function. The association between fitness and expression of certain HLA that present Pol epitopes suggests that immune-mediated mutations impairing viral fitness may play a key role in spontaneous control of HIV. Results indicate that HLA alleles responsible for such defects in protein function may differ among viral genes. Further identification of HLA-associated changes in HIV may allow design of vaccines targeting the most vulnerable regions of the virus.