Predicting the determinants of long-term HIV control with gene therapy strategies

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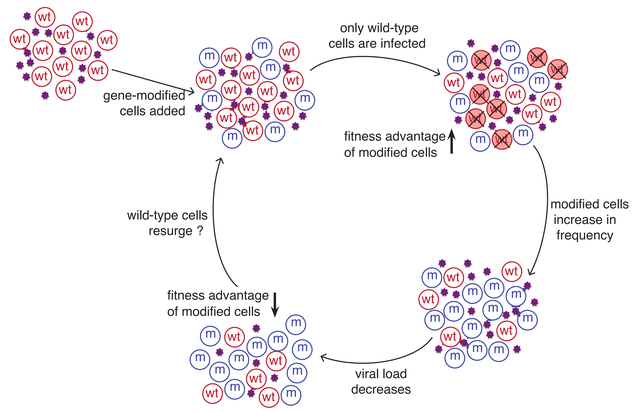
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Introduction

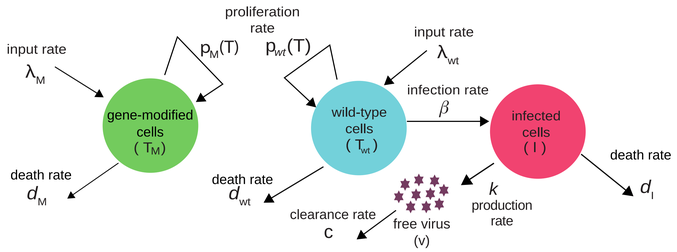
One proposed strategy to achieve long-term antiretroviral-free remission for HIV is to use gene therapy to render lymphocytes resistant to infection. Techniques have been developed to modify the CCR5 receptor[1] or the deliver antiviral gene products[2,3]. However, preliminary in vivo studies have had limited success in controlling the infection[4].

Here we develop a viral dynamics model to investigate the conditions under which genetically-modified cells have a sufficient selective advantage to reduce wild-type target cells below a critical density required to sustain ongoing HIV replication.

Concept:



Methods



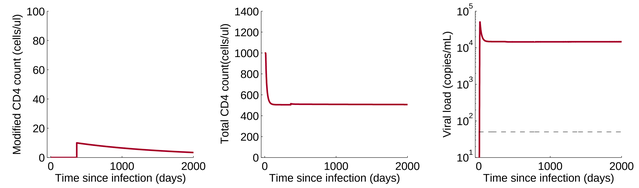
In our mathematical model, wild-type CD4$^+$ T cells can be produced by the thymus or homeostatic proliferation (density-dependent, half-max at $T=h$). An initial dose of genetically-modified cells – either CD4$^+$ T cells or hematopoietic stem cells – is transfused. Genetically-modified CD4$^+$ T cells can expand by homeostatic proliferation, or by input from progenitors (only if transplant includes stem cells). Wild-type and gene-edited cells compete for proliferation signals. Only wild-type cells are susceptible to HIV infection. The model was parameterized using data on lymphocyte kinetics and HIV dynamics[5-7].

Transplant with genetically-modified CD4$^+$ T cells

There are three possible outcomes of gene therapy, which depend on the function of the modified cells, the viral fitness, and the status of the recipient's immune system:

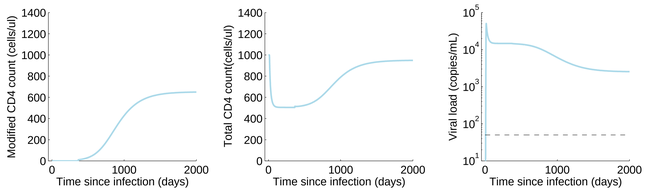
No engraftment

$p_M(T^*) < d_M$



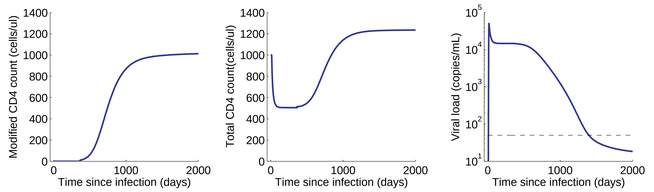
Sustained engraftment and viral load reduction

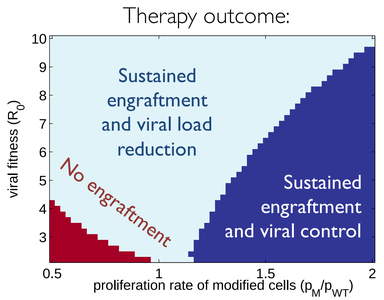
$p_M(T^*) > d_M$

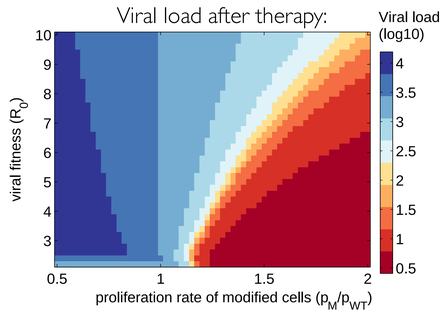


Sustained engraftment and viral control

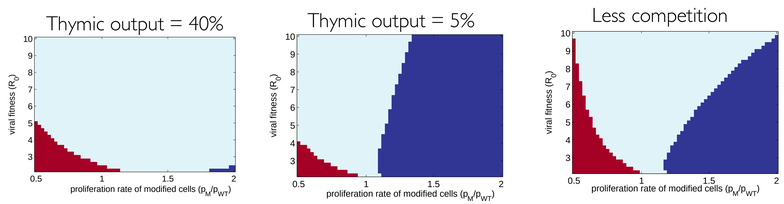
$R_0\, f_{WT} < 1$
and
$p_M/d_M > p_{WT}/d_{WT}$





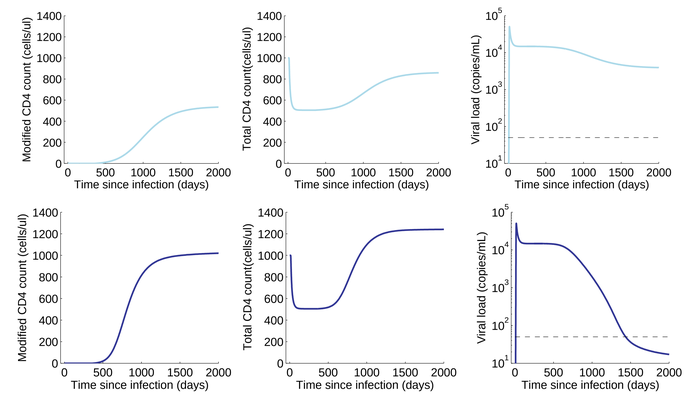


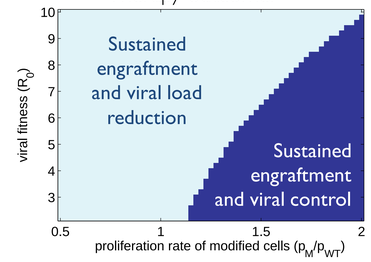
Engraftment and viral control are easier to achieve with lower thymic role in T cell maintenance (vs average ~10% at age ~35) and with more competition for homeostatic proliferation signals (described by cell level at which proliferation is half-max)

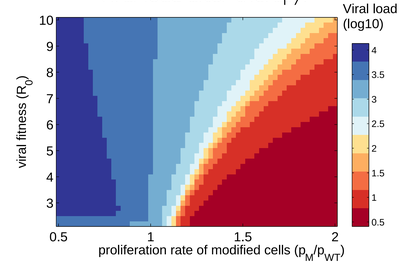


Transplant with genetically-modified stem cells

Modified hematopoietic stem cells are more likely to lead to sustained engraftment, even with impaired proliferative capacity, but are slightly slower to reduce viral load







Discussion

- The most likely outcome of gene therapy is that modified cells co-exist with wild-type cells below the level required to control HIV
- Engraftment requires modified CD4$^+$ T cells proliferate faster or live longer even in the absence of virus, or that modified stem cells be included
- Higher viral fitness can make it easier for modified cells to expand initially but harder to control infection
- Long ART interruptions are needed for high-level engraftment and control
- The benefit could be boosted if modified cells are also resistant to certain types of bystander cell death, or if they provide enhanced immune function

Acknowledgements

1. Holt N et al, *Nat Biotech*, 2010
2. Younan PM et al, *Blood*, 2013
3. DiGiusto DL et al, *Science Trans Med*, 2010
4. Tebas P et al, *NEJM*, 2014
5. Burg D et al, *J Theoretical Biology*, 2009.
6. den Braber et al, *Immunity*, 2012
7. Westera et al, *Aging Cell*, 2015

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