



Hematopoietic-Stem-Cell Based Therapy for HIV disease

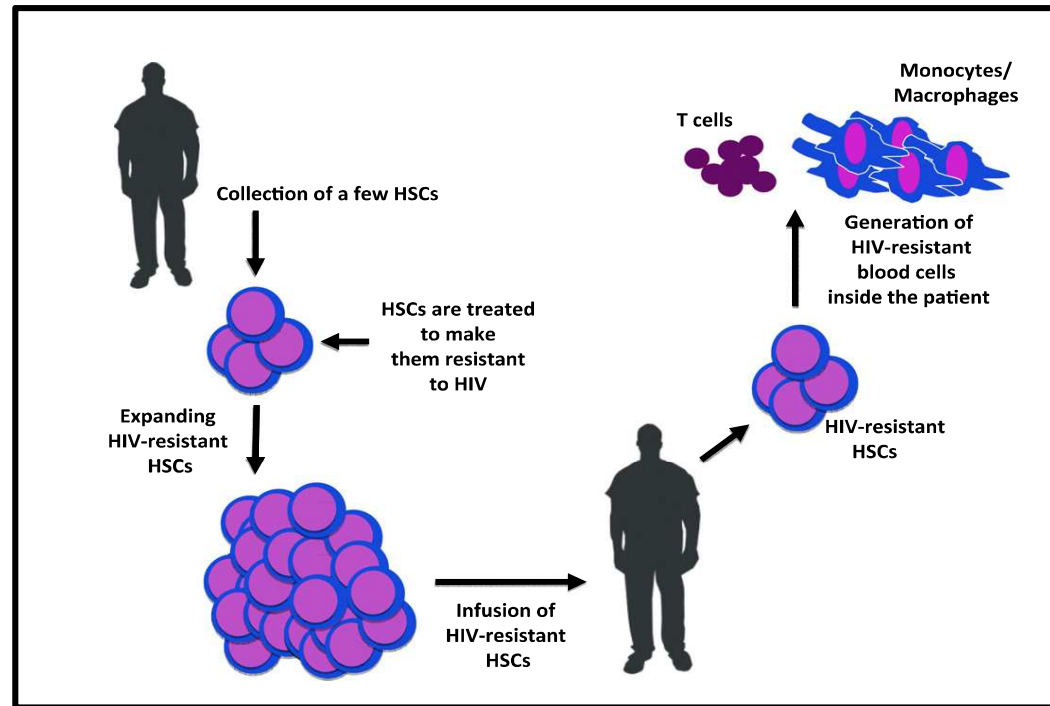
PROJECT OBJECTIVES AND MAIN ACTIVITIES:

Czech Genetic Bank will develop a novel platform to cure HIV disease. The major innovation is to use (i) hematopoietic stem cell transplantation of the cells resistant to HIV-1 harboring CCR5 $\Delta 32$ mutation widely spread in Norway. To prevent *graft-versus-host* disease (ii) regulatory T-cell mediated protection will be optimized using *gp120*.

TOTAL BUDGET: 1.000.000,- EUR, 2 researchers + 2 students

**MAIN OUTPUTS
AND RESULTS:** Creation of CCR5 $\Delta 32$ database for HSCs transplantation of
HIV resistant cells

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Long lived, self-renewing, multilineage hematopoietic stem cells (*HSCs*) modified such that their progeny resist HIV infection (such as *HSCs* from donor harboring *CCR5*Δ32 mutation). The host could thereafter be repopulated with a hematopoietic system (including CD4⁺ T cells and myeloid targets for HIV) that is resistant to the replication and spread of HIV (Kiem et al. 2012 Cell Stem Cell 10: 137-147).

Shaded Contour Map of $\Delta 32$ Allele Frequency Data

Novembre, J., et al PLoS Biology 3: e339

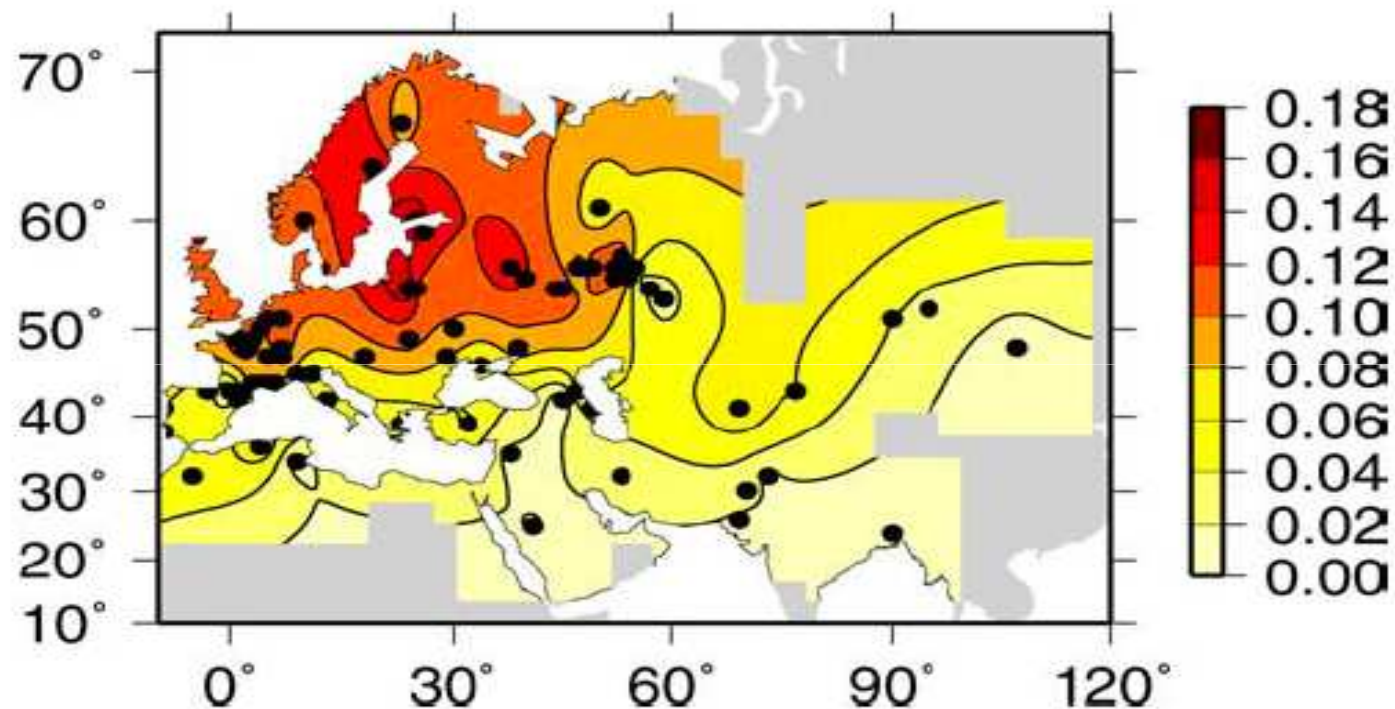
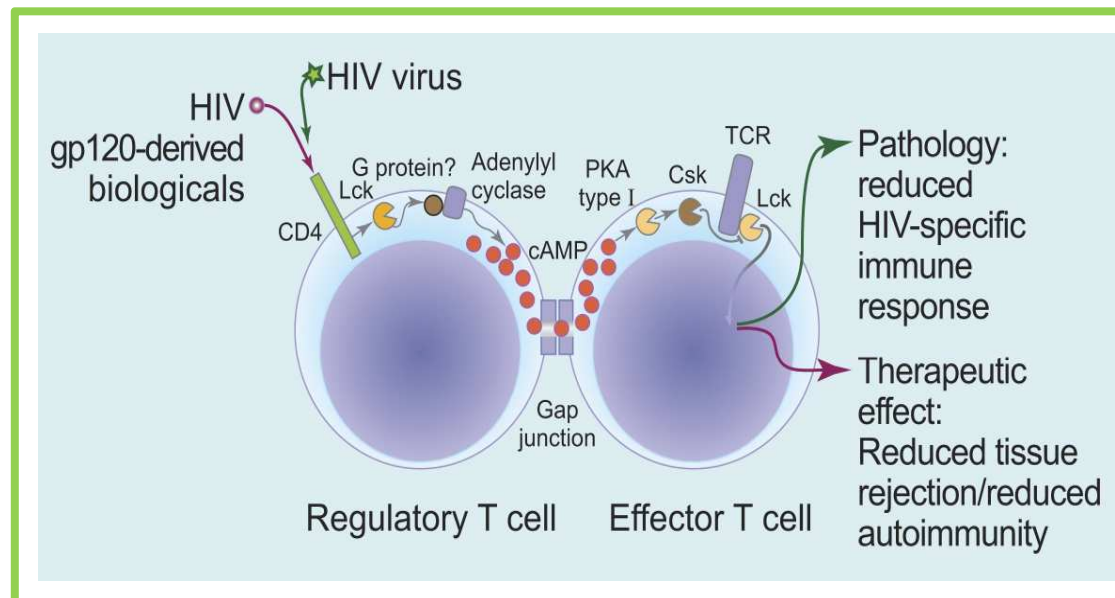


Figure 1. Shaded Contour Map of $\Delta 32$ Allele Frequency Data

The sampling locations are marked by black points. The interpolation is masked in regions where data are unavailable.

DOI: 10.1371/journal.pbio.0030339.g001

A schematic representation of regulatory T cell immunosuppression by cAMP following *gp120* ligation of CD4.



Upon triggering of CD4 on regulatory T cells by *gp120* protein or possibly *gp120*-derived agonists, Lck becomes active and turns on cAMP production by adenyl cyclase possibly through interaction with a G protein. cAMP is transferred from regulatory T cells to effector T cells through cell-to-cell contacts called GAP junctions that allow diffusion of small molecules down the concentration gradient and into effector T cells. Once inside effector cells, cAMP inhibits immune function through PKA-Csk inhibitory pathway that turns off T-cell activation proximally under the T-cell receptor in parallel with induction of potent inhibitor of cAMP-mediated transcription *ICER*. This could ameliorate *graft versus host* disease and lead to reduced tissue rejection and/or autoimmunity (adopted from Tasken, K. 2009, Blood 114: 1136-37).

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BANKA

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Therapy
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