Therapeutic modulation of immune responses in chronic HIV infection

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• **HIV infection**: Current concept of a chronic infection with complex pathophysiology
  – Not only a T cell disease

• **Therapeutic targets**
  – Host genetics
  – HIV-specific immunity
  – Gut «leakage» and chronic activation
HIV infects «activated» CD4+ T cells

(Commander «Cell in-chief» of immune responses)

Antigen encounter

Activation
Proliferation

Specialization
De novo production
- Cytokines (IFN-γ, IL-2)
- Crosstalk receptors
- Chemokine receptors

CD4 + T cell surface

CCR5
CD4
CXCR4
HIV-1

gp120

gp41

CD4: Primary receptor

CCR5 (chemokine R): Co-receptor

CD4:

CCR5

T cell surface
Which activated CD4 cells become infected in «primary» HIV infection?

• CD4+ T cells trying to combat HIV i.e. HIV-specific CD4+ T cells
  → inadequate primary immune response

• CD4+ T cells challenged 24/7
  → Gut mucosal CD4+ T cells (Th17 subset)
Primary HIV infection:
- Loss of HIV-specific CD4+ T cells
- Massacre of 75% of total body CD4+ cells, mainly in gut mucosa
  (few HIV-specific; Tiny fraction of blood CD4+ T cells)
HIV-1: Gut leakage to blood occurs

E. Coli DNA fragments

LPS / endotoxin

Jiang et al., JID 2009

Brenchley et al., Nat Med 2006
Trøseid et al., AIDS 2010
Chronic HIV infection: Complex dysequilibrium

- Partial immune control
- HIV-mutant escape
- HIV replication
- Intestinal leakage
- CD4-loss
- Chronic immune activation
- HIV tolerance
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Target #1: Host genetics

• GMP-manufactured, gene-modified bone marrow stem cells (Tebas et al., CROI 2011)
  – CCR5 co-receptor complete deletion (safe in 1-2% of norwegians)
    – Repopulate lymphoid tissue
    – New mature CD4 cells lacking CCR5 co-receptor outcompete over time «normal» CD4+ cells susceptible to HIV
  – No side effects (no chemotherapy needed)
**Target #2: HIV-specific immunity**

**Therapeutic vaccinations:**

**Opportunities**

- **Select candidates for a preventive HIV vaccine**
  (the only ethical way?)

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**The Vacc-4x story** (intracutanous HIV p24 Gag modified consensus peptides)

* Preliminary data (BionorPharma/OUH) → international multicentre trial
* Immunization in 90% (Kran et al., AIDS 2004, AIDS 2006, +)
* Systematic DTH skin test exploration (*in vivo test*) (Kvale et al., AIDS 2006)
* Negligible immune escape (Kran et al., AIDS 2010)
* Immune memory lasting 7.1 years (w/cytotoxic CD8+ T cells) (*submitted*)
* First reboost study (?) after 7 years completed (*in prep*)
* First in man (?) trial on nasal vaccination starting Oct 2011 (*completed Feb 2012*)
  (*OUH PI with BionorPharma & Eurocine*)
Target #2:
HIV-specific immunity

- Challenges I
  - Pitfall in measures for immunization in chronic infection

A. Lind et al. (submitted):
ART-naïve HIV+
Measures of «Total T cell suppression» to Gag and Env

Suppression neglected measure in evaluating boosting?

Speed / «activation» main parameter not f(engine) alone
Target #2: HIV-specific immunity

- Challenges II - Choice of HIV antigenic region(s) for vaccines
  - Gag (HIV inside) and not Env (HIV outside) T cell responses pronounced in slow progressors?
  - Wide variability in both Gag and Env responses

Rapid assay (degranulation) for Gag- and Env-specific CD8+ T cell responses:

**Env/Gag-ratios:**
Best factor in predicting CD4 loss (i.e. Progression, ART-naïve)

*(Pettersen et al., 2010)*
**Target #3: Gut «leakage» and chronic activation**

Example of translational research in OUH

HIV → Leakage of bacterial products → LPS → COX-2 → PGE2 → High cAMP

- **Taskén group UoO**
  - Dysfunctional T cell

**First in man trials at OUH of COX-2 inhibitors in HIV:**

* Reduced activation (=reduced progression rate?) in patients on ART (Kvale et al., AIDS 2006)

* in ART-naïve (Pettersen et al., J Virol 2011)

* Improved vaccine responses in ART-naïve (Pettersen et al., J Virol 2011)

* New ongoing trial testing long vs short COX-2i (Trøseid/Reikvam)

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