Unraveling TB/HIV-1 Host Pathogen Interactions: *Integrating Molecular Approaches and Patient Care*

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TB and HIV infection each result in a host immune response, which in turn influences the natural progression of the other pathogen.

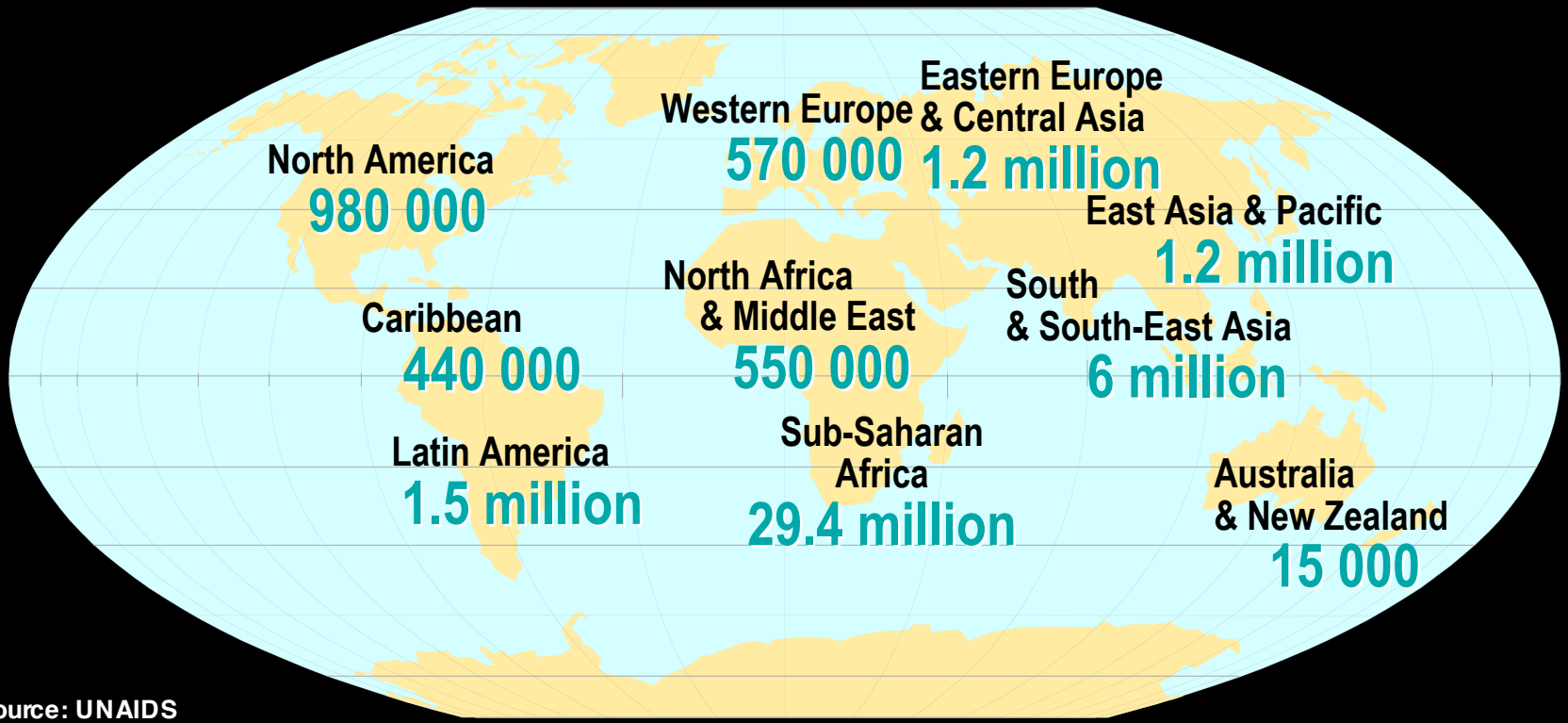
MTb infection and clinical disease is thought to accelerate the course of HIV infection causing shorter survival due to induction of higher viral loads in co-infected HIV-infected patients.

Pape et al. 1993; Whalen et al. 1995; Day et al. 2004

HIV-1 infection and clinical disease dramatically increases the risk of both reactivation and progression of primary TB infection

Vallarion et al. Morb Mort Wkly Report 1992

Distinct Host Immune Factors and Pathogen Strains



Source: UNAIDS

? Host and ethnic specific responses to initial infection and then progression of disease due to each pathogen

2 diseases, 1 patient

?Geographic (strain/specific effects) of each pathogen upon the immune response, *and hence upon each other*

HIV-1

HIV-1 subtypes have spread unevenly such that the B subtype is associated with infection in the North and C and E have spread in Africa and Asia (the most heavily TB burdened) and are currently the most prevalent and rapidly spreading subtypes

The relationship between HIV-1 subtype and pathogenicity alone or in TB co-infection largely unknown

However:
Representative E subtype LTRs less responsive to TNF
and C subtype LTRs more responsive to Tat and p65
Montano et al .1997 &1998 J. Virol, Lemieux et al. 2004 JBC

Tat from subtype E differentially inhibits TNF
Ranjbar et al. Abstract # MoPe14.2B04

? Role of HIV-1 diversity in TB/HIV-1 co-infection

TB:
MTb infection, viral load and HIV-1 disease progression

MTb infection directly induces HIV replication *in vitro*….
and viral load is higher in HIV-1 infected patients with active TB.

Zhang et al. JCI 1995; Shattock et al. J. Gen. Virol.1994;
Lederman et al. JAIDS 1994; Goletti et al. J.I. 1996;
Toosi et al. Clin Exp Imm 2001

MTb induces preferential CXCR4 on alveloar macrophages and X4 HIV-1 replication.

Hoshino et al. J.I., 2004

Different TB strains have different phenotypes with respect to their virulence and ability to cause disease in mice. MTb isolates of the W-Beijing family correlated with different cytokine profiles

Manca et al JI 1999 and PNAS 2001; *Reed et al, Nature 2004*

? Role of distinct MTb strains in modulation of HIV-1

Host Genetics and HIV Infection

Gene mutations leading to natural resistance to HIV infection

- CCR5 delta 32 mutation (Liu R et al, Cell 1996; Samson M et al, Nature 1996)
- CCR2 mutation (Kostrikis LG et al, Nat Med 1998)
- SDF-1 mutation (Winkler C et al, Science 1998)
- Chemokine receptor CX_3CR1 mutation (Faure S et al, Science 2000)

HLA associations associated with rate of progression to AIDS

- Rapid progression
  - HLA Class I homozygosity (Carrington M et al, Science 1999)
  - HLA-B35 (Kaslow et al, Nat Med 1996; Gao et al, NEJM, 2001)
- Slow progression
  - HLA-B*27 and B*57 (Kaslow et al, Nat Med 1996; Migueles SA et al, PNAS 2000)
  - HLA-Bw4 homozygosity (Flores-Villanueva, PNAS 2001)

TB and HLA

TB susceptibility and HLA-DR2 serotype.

- Brahmajothi et al., Tubercle 1992 (India);
- Ravikumar et al., Tuber Lung Dis 1999 (India);
- Bothamley et al., J Infect Dis 1989 (Indonesia);
- Khomenko et al., Tubercle 1990 (Russia);
- Teran-Escandon et al., Chest 1999 (Mexico);
- Dubaniewicz et al., Int J Infect Dis 2000 (Poland)

TB susceptibility and a specific HLA gene association.

- Goldfeld et al., JAMA 1998: HLA-DQB1*0503 (Cambodia)

Photo: James Nachtwey

HLA class II molecules are responsible for the presentation of MTb antigens to effector T-cells which control clinical TB disease after infection with MTb rendering disease latent and can be measured by a delayed-type hypersensitivity (DTH) response to intradermal injection of PPD most routinely used TB screening tool including in HIV co-infection.

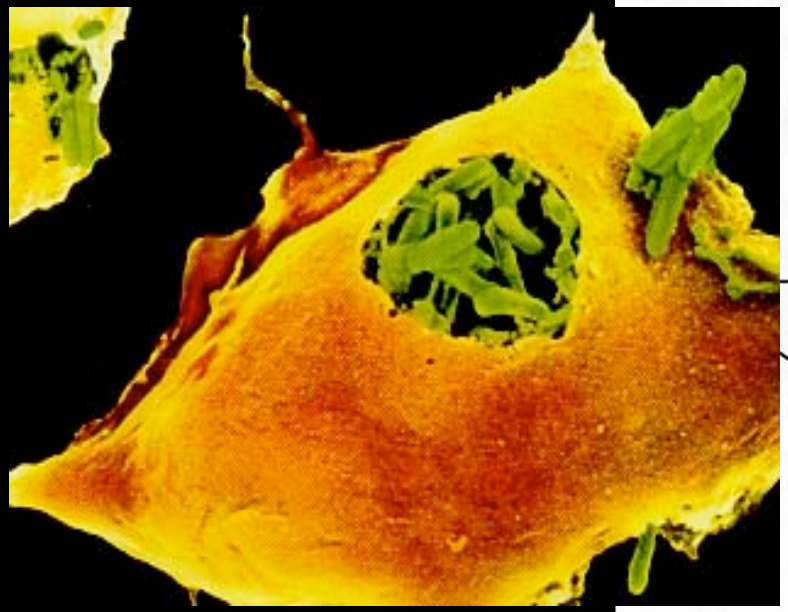
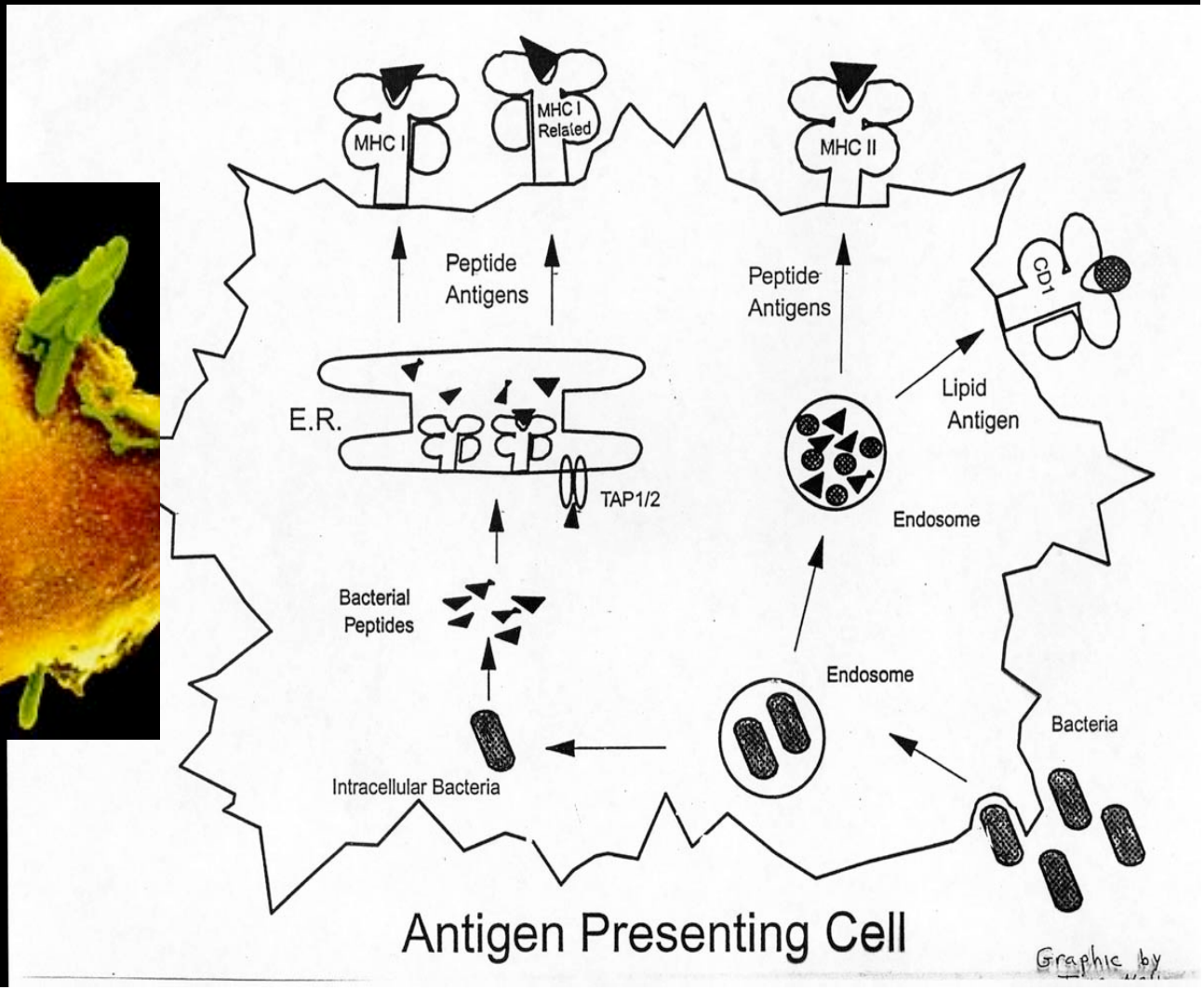
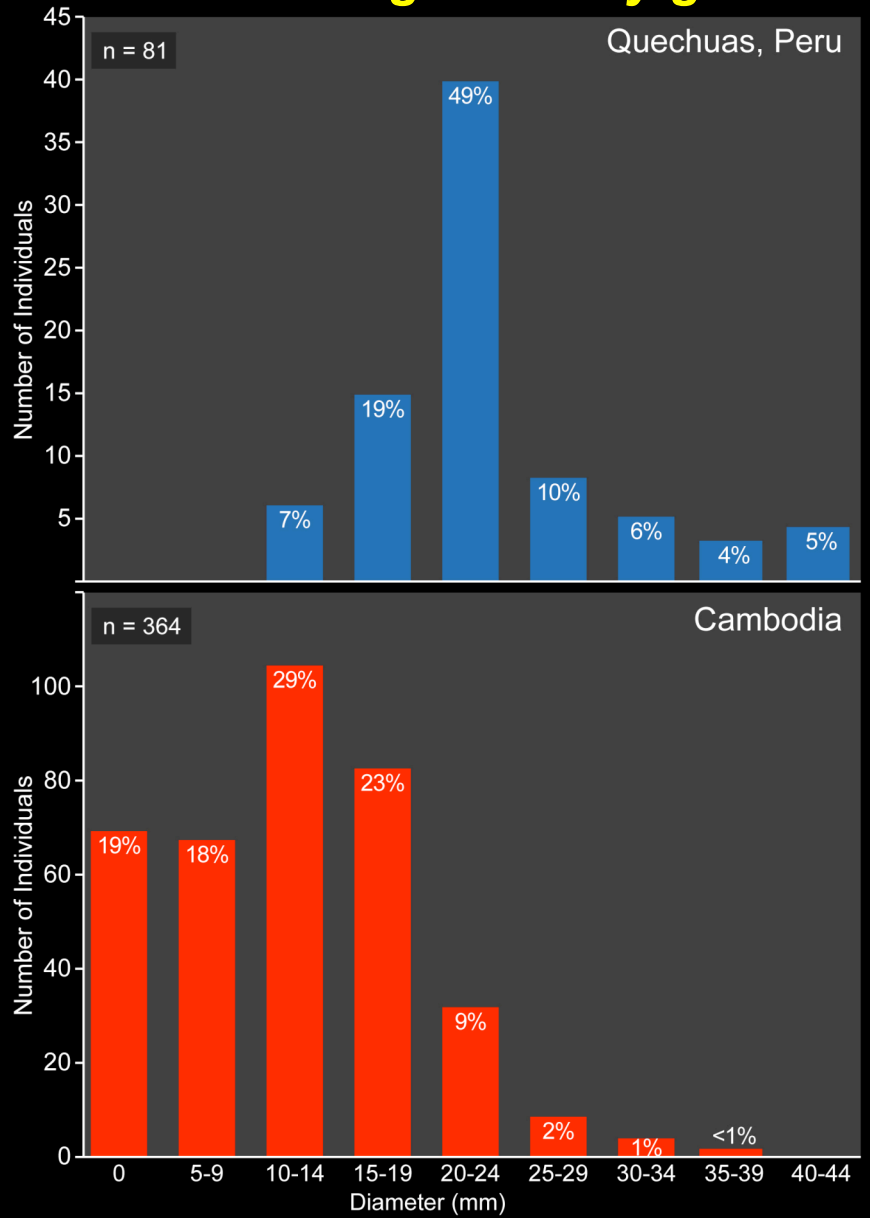


Photo courtesy of SHE Kaufman



Impact of Ethnicity upon DTH responses:

PPD Sizes in AFB+ PTB Patients from the Peruvian Andes are significantly greater than in Cambodians



Of 81 Quechuan PTB patients PPD-tested, No anergics found *as compared to 19% of 364 Cambodian PTB patients*

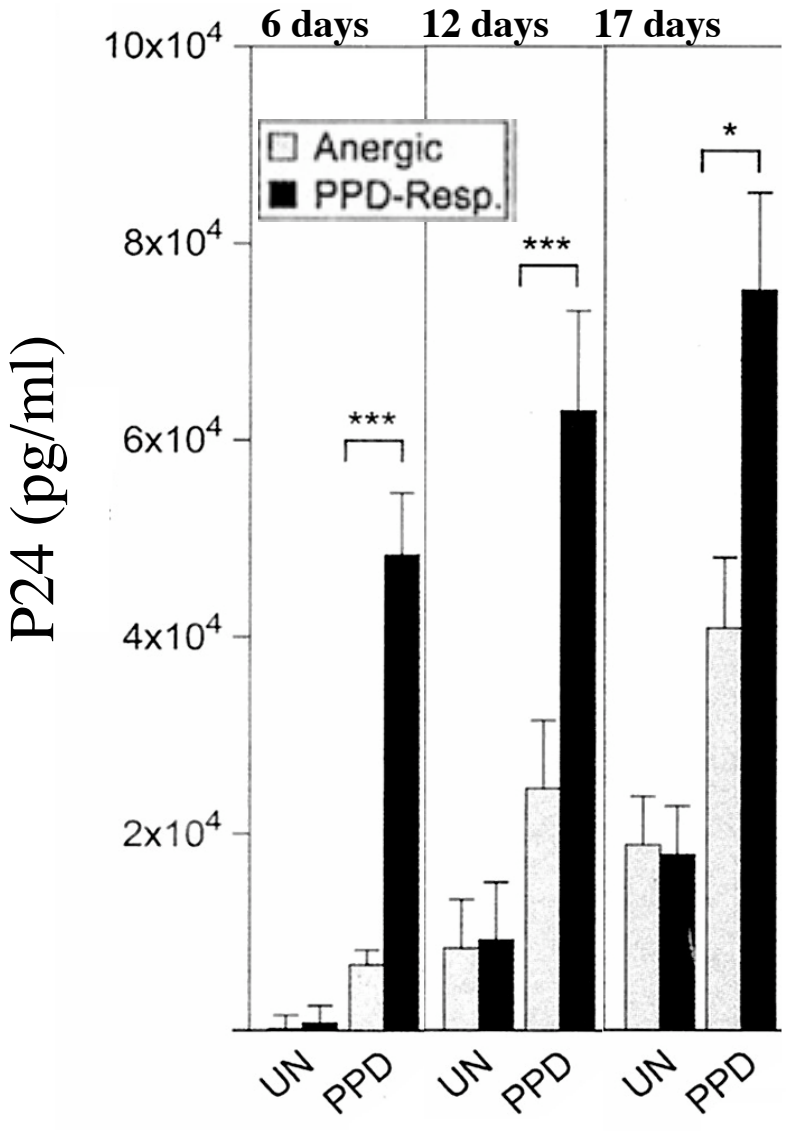
Peruvian Quechuas:
aver. PPD size: 21.69 mm +/- 5.46
74% of 81 PPD>20 mm

Cambodians:
aver. PPD size: 11.42 mm +/- 7.74
13% of 364 PPD>20 mm

P<0.0001

Delgado et al, IJTLD 2004

? Impact of antigen specific DTH to TB upon HIV-1 Replication *in vitro*

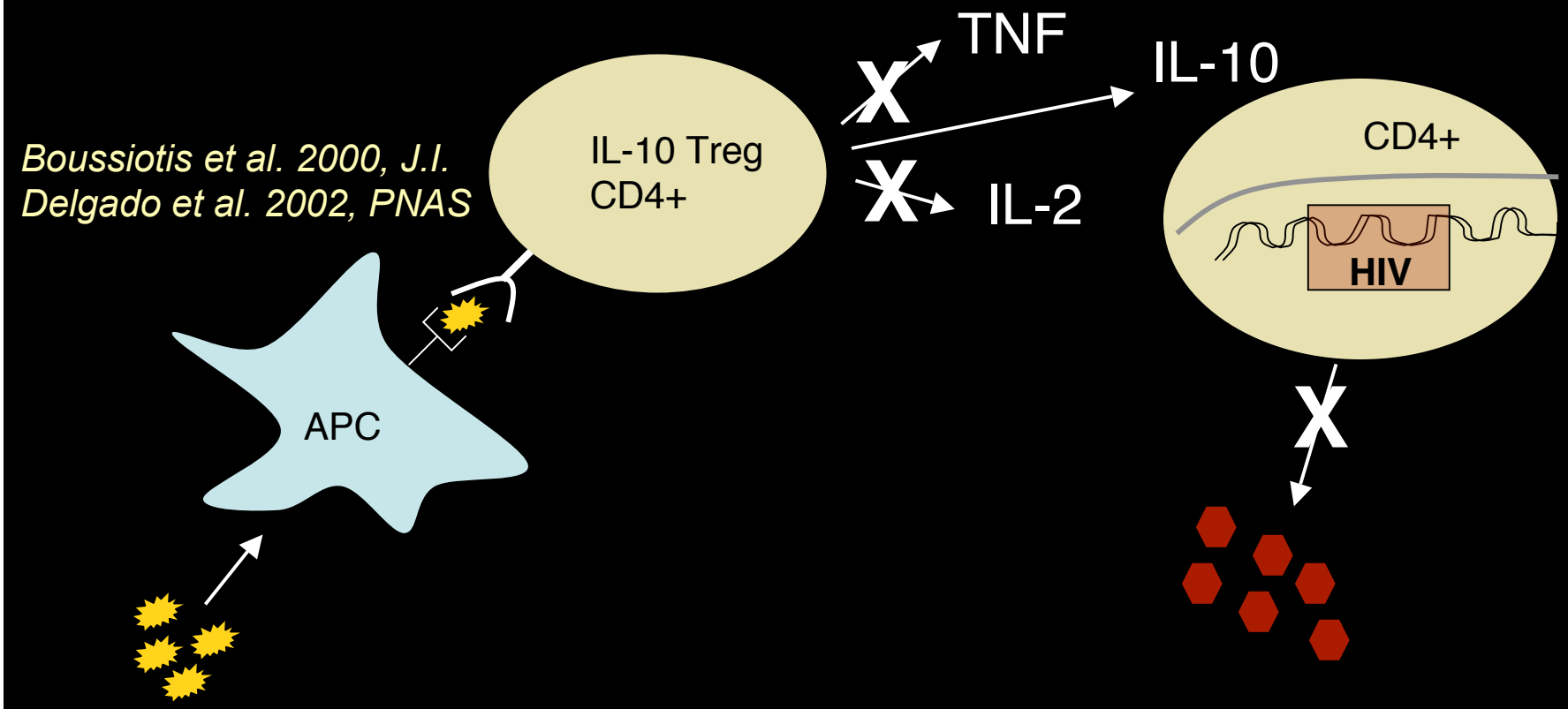


Replication of a T-tropic primary HIV-1 isolate is impaired in PPD-anergic as compared with PPD-responsive donor cells

Ranjbar et al. 2004, J.I.

Host specific T cell responses (DTH) to MTb influence HIV replication:

In anergic donors, the cytokine milieu is different post-MTb challenge and does not favor HIV replication



HIV/TB in Children: Impact of host factors on disease progression unknown

Photo: James Nachtwey

? Immune indicators that influence progression of TB/HIV outcome

studies of immune reconstitution in resource poor settings limited

? Optimal timing of ARVs using a PI-sparing regimen & immunological and virological markers of success and the impact of TB

Cambodia has one of the highest TB burdens globally:
10 highest incidence countries (per 100,000)

	Incidence	Prevalence
1. Cambodia	539	963
2. Zimbabwe	538	626
3. South Africa	392	604
4. Indonesia	385	786
5. Afghanistan	333	753
6. Uganda	320	451
7. Philippines	314	693
8. Tanzania	308	396
9. Kenya	297	371
10. Peru	265	288

Data from Dye et al. "Consensus Statement on the Global Burden of TB", JAMA Aug.1999

AIDS in Cambodia: First HIV-1+ individual detected in 1991 first AIDS case 1993

HIV-1 infection in Cambodia currently the highest in southeast Asia (~1.9-2.6% of 15-49 yo)

Cambodian Health Committee: A Transferable model

Clinical Operational: **Significant improvements in TB case detection, compliance, cure rates in one of the world's most resource poor rural environments using strategies including patient supporters, HOME DOTs and microcredit**

Sok Thim et al., 2004 JAMA

Which Facilitates Scientific and Clinical Research **into basic immunopathogenesis because of the stable agarian patient base and long term commitment of staff and patients.**

Photo: James Nachtwey

Leveraging successful CHC TB strategies to introduce HAART in rural Cambodia

Abstract # MoP311.2C08

CHC TB Program:

June 1994-December 2004

Svay Rieng

and Kampot Provinces:

<u>4734 Cured</u>

Partners: NTP, JICA

July 2004-May 2005

CHC AIDS Program:

Svay Rieng

<u>499 in follow-up</u>

190 on HAART/309 on OI Rx

Kampot:

<u>274 in follow-up</u>

147 on HAART

127 on OI Rx

Partners: NCHADS MSF-F & B, TREAT Asia,

Building a TB and HIV-1 clinical and research network in Cambodia

Supported by:

NIH-CIPRA (Comprehensive International Program for Research on AIDS)

ANRS (*Agence National sur Recherches du SIDA*),

Sok Thim, Delfraissy,

Laureillard, Barre-Sinoussi,

Blanc, Glaziou, Borand, Rekacewicz, L'her,

Leroy-Terquem, Mayoud, Kazatchkine, Sarthou,

Mean Chhi Vunh, Goldfeld

Bazin, Hoff, Near, Laughon, Fanning

Creating Centers of Urban and Rural Excellence for HIV/TB care and research in Cambodia:

- Clinical research into optimal TB/HIV treatment CAMELIA trial (Cambodian early vs. late introduction of ARVs in immunosuppressed AIDS patients with TB). Provide ARVs for 660 patients and a venue for training Cambodian clinicians and researchers

- Integration of research into basic mechanisms of TB/AIDS immunopathogenesis including host and pathogen signatures diagnostic of infection, TB cure, & paradoxical reactions

- Development of operational models of delivery of care building upon CHC TB programs and creating models for performing clinical and basic studies transferable to other resource poor settings

CAMELIA: (ANRS/CIPRA)

CAMbodian Early vs Late Introduction of Antiretrovirals

Early (2 weeks) *vs.* late (2 months) introduction of HAART in naïve HIV-infected adults with TB in Cambodia and CD4<200

Rationale:

- The degree of immunosuppression is the most Important predictor of survival in HIV-1-infected individuals with TB
  Havlir and Barnes, NEJM 1999; Whalen et al. Am. J. Crit. Care Med, 1996
- MTb increases HIV-1 replication *in vivo* and in *in vitro* models
  Goletti, Fauci et al., Jl 1996; Ranjbar et al. 2004
- TB treatment alone did not decrease viral load in patient with low CD4
  Wolday et al. IJTLD 1996

HYPOTHESIS:

The initiation of HAART at 2 weeks will result in a lower mortality rate than the delayed arm in patients with very low CD4+ T cell counts

prospective randomized two-armed trial with no placebo
660 patients randomized; 330 per arm from rural and urban sites

Leverage resources of a clinical trial (human capacity and drugs to provide treatment: ***CAMELIA (ANRS) will provide drugs for 660 for 2 years***

Photo: James Nachtwey

Integration of Basic Scientific Discovery:
Determine Immune function, host and pathogen signatures in TB and AIDS co-infection

CAMELIA also provides a unique opportunity to understand the basic immunopathogenic mechanisms in TB/HIV co-infection

Scientific Goals:

To determine the best approach to treat TB/AIDS co-infection and avoid adverse reactions

To understand the immunological mechanisms underlying success or failure of therapy to lead to novel targets for immunomodulatory therapy

Determine Immune function, host and pathogen signatures in TB and AIDS co-infection

Specifically, we will determine:

(i) Immune correlates (immune signatures) of TB outcome (cure, persistent bacteremia, death)

(ii) Immune correlates of HIV-1 outcome (immune reconstitution or failure,and success or failure of control of viremia

(iii) Immune correlates of paradoxical reactions observed in a subset of patients upon immune reconstitution

(iv) MTb correlates (MTb signatures) of TB outcome (cure, persistent bacteremia, death)

Short term goals for discussion

These goals are directed towards maximizing existing knowledge to discover novel and immediately applicable approaches for cure of TB and control of HIV in adults and children.

- Determine the optimal timing of introduction of ARVs in TB/HIV co-infected adults and children receiving TB therapy

- Determine pediatric immune profiles that influence progression of HIV and TB/HIV outcome

- ***Maximize the global impact of clinical trials by integrating basic scientific discovery of host and pathogen factors correlated with or determining clinical outcome***

Long term goals for discussion

These goals are directed towards understanding host and pathogen factors that will allow:

(i) targeted drug development including immunotherapeutic approaches to co-infection

(ii) Identification of patients who will benefit from specific therapeutic approaches or who are at risk for adverse events

Determine the impact of ethnic specific host genetic factors in TB/HIV pathogenesis and clinical outcome in adults and children

Determine the impact of HIV-1 clade specificity upon HIV/TB pathogenesis and clinical outcome

Determine the impact of MTb strain specificity upon HIV/TB pathogenesis and clinical outcome

Cambodian /US/ French cooperative model to provide:
Service,Capacity building, Clinical answer,Scientific discovery

CHC/CBR Research Group: *Shahin Ranjbar, Julio Delgado, Adrienne Shapiro,Sun Sath, K.K. Lak, Meas Sina,*

Sok Thim

Didier Laureillard

Photo: James Nachtwey

Photo: Malcolm Linton

Partners/Collaborators:
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Leroy-Terquem, Mayoud, Kazatchkine, Sarthou, Mean Chhi Vunh