3rd Annual RePORT International Meeting
Pestana Rio Atlantica Hotel
Rio de Janeiro – September 12 & 13 2017

Immunopathogenesis of M.tb Infection and TB in Brazil

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Immune Function in Young Children With Previous Pulmonary or Miliary/Meningeal Tuberculosis and Impact of BCG Vaccination

Timothy R. Sterling, MD[a], Terezinha Martire, MD[b,c], Alexandre Silva de Almeida, PhD[b], Li Ding, MD[d], David E. Greenberg, MD[d], Lorena Alves Moreira, MS[b], Houda Elloumi, PhD[d], Angelica P. V. Torres, RN, BSN[b], Clemax Couto Sant'Anna, MD, PhD[e], Eliane Calazans, MD[f], Geraldo Paraguassu, MD[g,h], Tebeb Gebretsadik, MPH[i], Ayumi Shintani, PhD, MPH[i], Kathleen Miller, RN, BSN[a], Afranio Kritski, MD, PhD[b], Jose Roberto Lapa e Silva, MD, PhD[b], Steven M. Holland, MD[d]

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Abnormal Immune Responses in Persons with Previous Extrapulmonary Tuberculosis in an *In Vitro* Model That Simulates *In Vivo* Infection with *Mycobacterium tuberculosis*

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frontiers in Microbiology

Transcriptomic Biomarkers for Tuberculosis: Evaluation of *DOCK9*, *EPHA4*, and *NPC2* mRNA Expression in Peripheral Blood

Leonardo S. de Araujo[1], Lea A. I. Vaas[2], Marcelo Ribeiro-Alves[3], Robert Geffers[4], Fernanda C. Q. Mello[5], Alexandre S. de Almeida[6], Adriana da S. R. Moreira[5], Afrânio L. Kritski[5], José R. Lapa e Silva[5], Milton O. Moraes[6], Frank Pessler[2,4†] and Maria H. F. Saad[1*†]*

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October 2016 | Volume 7 | Article 1586

THE JOURNAL OF IMMUNOLOGY

Tuberculosis Is Associated with a Down-Modulatory Lung Immune Response That Impairs Th1-Type Immunity

Alexandre S. Almeida, Patrícia M. Lago, Neio Boechat, Richard C. Huard, Luiz C. O. Lazzarini, Adalberto R. Santos, Marcelo Nociari, Hongxia Zhu, Beatriz M. Perez-Sweeney, Heejung Bang, Quanhong Ni, Jie Huang, Andrea L. Gibson, Vera C. Flores, Lorena R. Pecanha, Afrânio L. Kritski, José R. Lapa e Silva and John L. Ho

J Immunol 2009; 183:718-731; Prepublished online 17 June 2009;

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Increased Frequency of Regulatory T Cells and T Lymphocyte Activation in Persons with Previously Treated Extrapulmonary Tuberculosis

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Published in final edited form as:
Int J Tuberc Lung Dis. 2012 May ; 16(5): 656–659. doi:10.5588/ijtld.11.0707.

Interleukin-10 and interferon-gamma patterns during tuberculosis treatment: possible association with recurrence

P. M. Lago[*], **N. Boéchat**[*], **D. P. Migueis**[*], **A. S. Almeida**[*], **L. C. Lazzarini**[*], **M. M. Saldanha**[*], **A. L. Kritski**[*], **J. L. Ho**[†,‡], and **J. R. Lapa e Silva**[*,†]

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Nature. 2010 Aug 19;466(7309):973-7. doi: 10.1038/nature09247.

An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis.

Berry MP, Graham CM, McNab FW, Xu Z, Bloch SA, Oni T, Wilkinson KA, Banc

Correlates of tuberculosis risk: predictive biomarkers for progression to active tuberculosis

Elisa Petruccioli[1], Thomas J. Scriba[2,3], Linda Petrone[1], Mark Hatherill[2,3], Daniela M. Cirillo[4], Simone A. Joosten[5], Tom H. Ottenhoff[5], Claudia M. Denkinger[6] and Delia Goletti[1]

Eur Respir J 2016; 48: 1751–1763 | DOI: 10.1183/13993003.01012-2016

plex

infections and biomarkers of Th2-type inflammation

Tuberculosis 102 (2017) 68–75

DIAGNOSTICS

Multiple cytokine responses in discriminating between active tuberculosis and latent tuberculosis infection

Jing Wu [a, 1], Sen Wang [a, 1], Chanyi Lu [a], Lingyun Shao [a], Yan Gao [a], Zumo Zhou [b], Heqing Huang [b], Ying Zhang [a, c, d, e, *], Wenhong Zhang [a, c, d, *]

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Jayne S. Sutherland[1]
[1]Vaccinology Theme, Medical Research Council Unit, Fajara, the Gambia. [2]DST/NRF Centre of Excellence for Biomedical Tuberculosis Research and MRC Centre for Molecular and Cellular Biology, Division of Molecular Biology and Human Genetics, Dept of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa.

PLOS | ONE

RESEARCH ARTICLE

The Transcriptional Signature of Active Tuberculosis Reflects Symptom Status in Extra-Pulmonary and Pulmonary Tuberculosis

Simon Blankley[1], Christine M. Graham[1], Jacob Turner[2], Matthew P. R. Berry[1,3], Chloe I. Bloom[1], Zhaohui Xu[4], Virginia Pascual[4], Jacques Banchereau[5], Damien Chaussabel[6], Ronan Breen[7], George Santis[7,8], Derek M. Blankenship[2], Marc Lipman[9,10], Anne O'Garra[1,11]*

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Citation: Blankley S, Graham CM, Turner J, Berry

International Journal of Infectious Diseases 56 (2017) 253–257

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

A tuberculosis biomarker database: the key to novel TB diagnostics

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Objective

The aim of the Biomarkers project was to discover relevant biomarkers for distinction of Latent and active Tuberculosis (acquisition of infection, progression from infection to disease) that could be used in clinical practice as well as for the evaluation of new drugs or regimens, new vaccines or new surveillance tools.

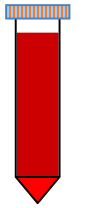
✓ Identify new Biomarkers candidates

Methodology

Patients at T0 → Household Contacts at T0 → 4 -6 Months → Household Contacts at T4+ → Household & Patients 2 Years after treatment

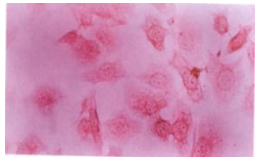
Serum/ Plasma

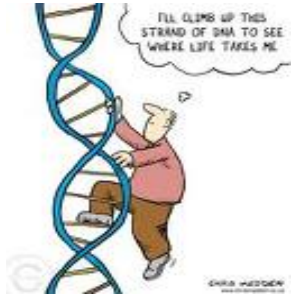
Blood



RNAm

PBMC's





Cohort 1 – Guadalupe/RJ (2012 -2015)

TB Patients → **74 individuals**

Household Contacts → **73 individuals**

147 individuals analyzed

Cohort 2 – UFRJ (2012-2014)

TB Patients → **7 individuals**

Household Contacts → **62 individuals**

69 individuals analyzed

Experimental design Reanalysis of Genes Differentially Expressed (GDE's) 2012

Different studies
M.tb

Sel. and obtaining data from Mycobacterium tuberculosis (GEO)

Data Baks from the Gene Expression Ominibus (GEO)

GSE11199 GSE25534

GSE31348; GSE36238

GSE28623

E-GEOD-19491; E-GEOD-19443; E-GEOD-19442

Software Estatístico *R*

Creation of the expression sets

Statistical Reanalysis

Sel criteria from GDE's for reanalysis

P value Adjusted

P value Adjusted ≤ 0,05
Log Fold Change >1

Graphics, Diagrams & GDE's spread sheets

Log Fold Change > or <1

Selection of potential Biomakers

Synthesis of 86 Primers

Total de 181 Biomarkers candidates

Interview with contact and / or the patient – Guadalupe RJ

Sample collection in PAXGENE

RNA Extraction at FIOCRUZ RJ

cDNA

cDNA Pré amplification

Análise do dado Bruto de Expressão

Statistical Software *"R"*

General analysis of clusters

P valor Ajustado <0,1 - 0,05

Table 1. Demographic, clinical data of all **COHORT 1** subjects at the time of diagnosis.

Clinical Charactheristics	Features	TST-	TST+	TB	*P.value*
Age	*Years*	35 (23.6) 38 (IQR=26.5)	38 (25.7) 41 (IQR=29.25)	74 (50) 40 (IQR=20.75)	0,8681
Gender	*Male*	10 (6.8)	12 (8.1)	47 (31.8)	2e-04
	Female	25 (16.9)	26 (17.6)	27 (18.2)	
Sputum Smear microscopy	*Neg*			20 (13.5)	1
	Pos			54 (86.5)	
TB Culture	*1*			5 (3.4)	1
	2 +			32 (20.1)	
Time of Cough	*Weeks*			8 (IQR=9)	0,7087
Cavity	*No*			14 (9.5)	
	Yes			46 (31.1)	
Treatment Outcome	*Defaulting*			11 (7.4)	
	cure			47 (31.8)	
	Death			2 (1.4)	

Sociodemographic, clinical and laboratorial characteristics of the household contacts (TST-, n=35), latent tuberculosis infection (TST+, n=38) patients, and active tuberculosis (TB, n=74) patients in the cohort 1.

Table 2. Demographic, clinical data of all **COHORT 2** subjects at the time of diagnosis.

Clinical Charactheristics	Features	TST-	TST+	TB	P.value
		22 (31.9)	40 (58)	7 (10.1)	
Age	Years	43.5 (IQR=29.75)	43 (IQR=21.75)	52 (IQR=7)	0,0786
Gender	Male	7 (10.1)	14 (20.3)	3 (4.3)	0,8699
	Female	15 (21.7)	26 (37.7)	4 (5.8)	
Acid Fast Bacilli	0			2 (2.9)	1
	1 +			3 (3.2)	
TST Convertors		4 (5.8)			

Sociodemographic, clinical and laboratorial characteristics of the household contacts (TST-, n=22), latent tuberculosis infection (TST+, n=40) patients, and active tuberculosis (TB, n=7) patients in the cohort 2.

Figure 1.

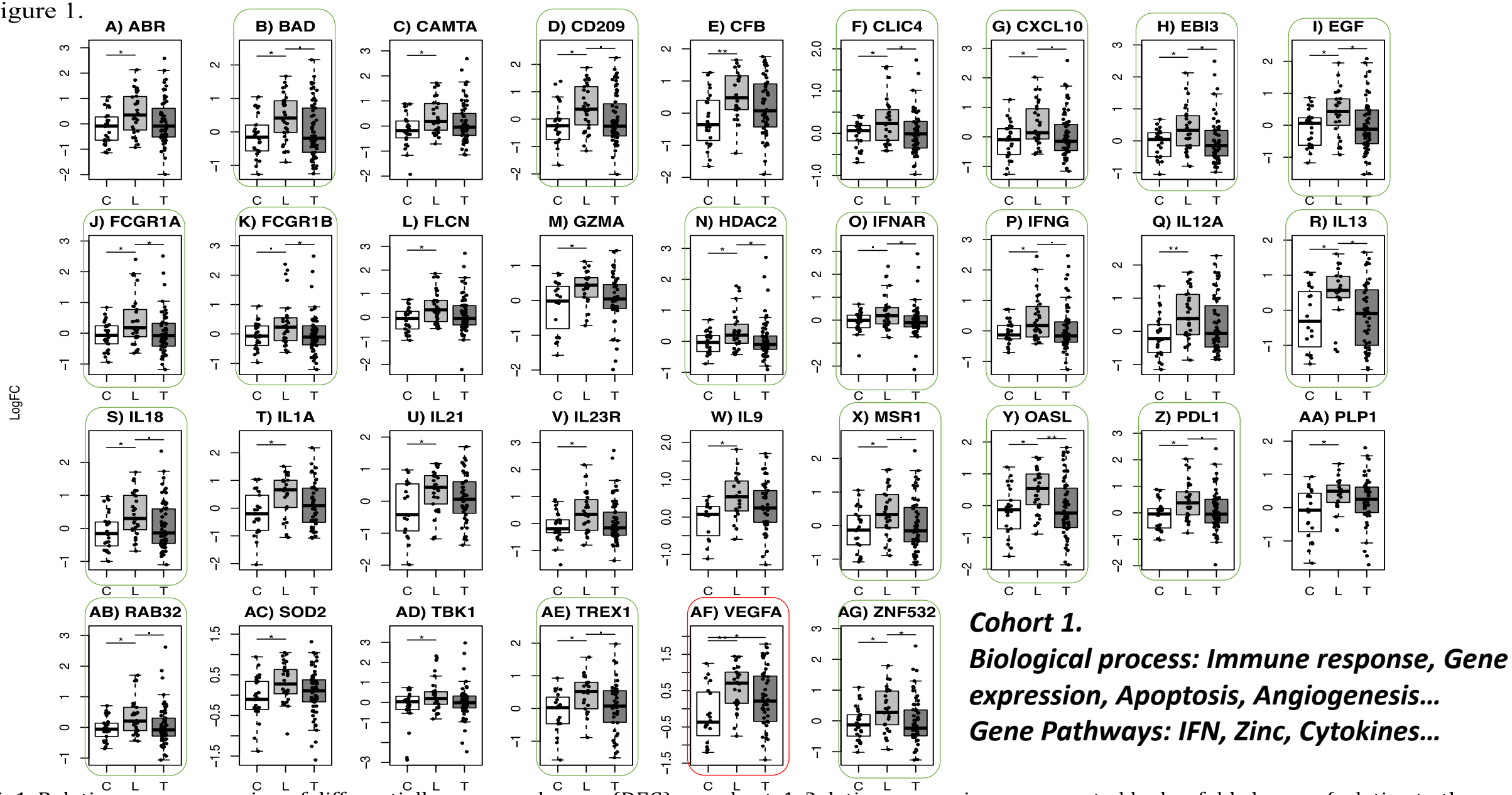
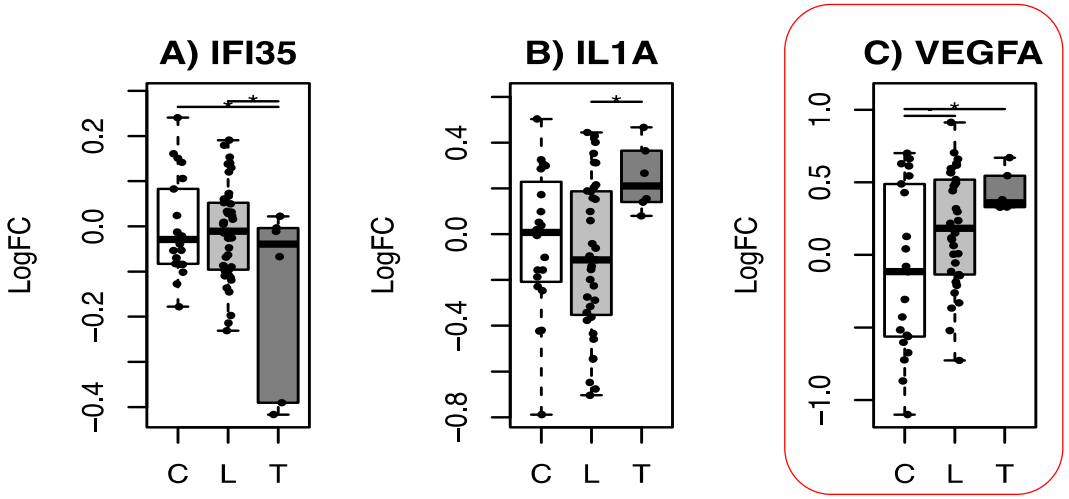


Fig1. Relative gene expression of differentially expressed genes (DEG) on cohort 1 Relative expression, represented by log-fold changes (relative to the mean normalized expression of household contacts (C)), of 33 DEG. C = household contacts (TST-)(white, n=35), L = latent tuberculosis infection patients (TST+) (lightgray, n=38), T = active tuberculosis patients (TB)(darkgray, n=74). Central bar indicates the median log-fold changes, while boxes boundaries indicate the interquartile range. Black dots represents each contact/patient in the cohort (n=147). Statistical significance symbols: "." = p-value < 0.1, "*" = p-value <= 0.05, "**" = p-value <= 0.01.

Cohort 2

Figure 2.



Same way of mRNA expression as in the cohort 1…

Fig2. Relative gene expression of differentially expressed genes (DEG) on cohort 2. Relative expression, represented by log-fold changes (relative to the mean normalized expression of household contacts (C)), of 3 DEG. C = household contacts (TST-)(white, n=22), L = latent tuberculosis (TST+) (lightgray, n=40) infection patients, T = active tuberculosis patients (TB) (darkgray, n=7). Central bar indicates the median log-fold changes, while boxes boundaries indicate the interquartile range. Black dots represents each contact/patient in the cohort (n=?). Statistical significance symbols: "." = p-value < 0.1, "*" = p-value <= 0.05, "**" = p-value <= 0.01.

Figure 3.

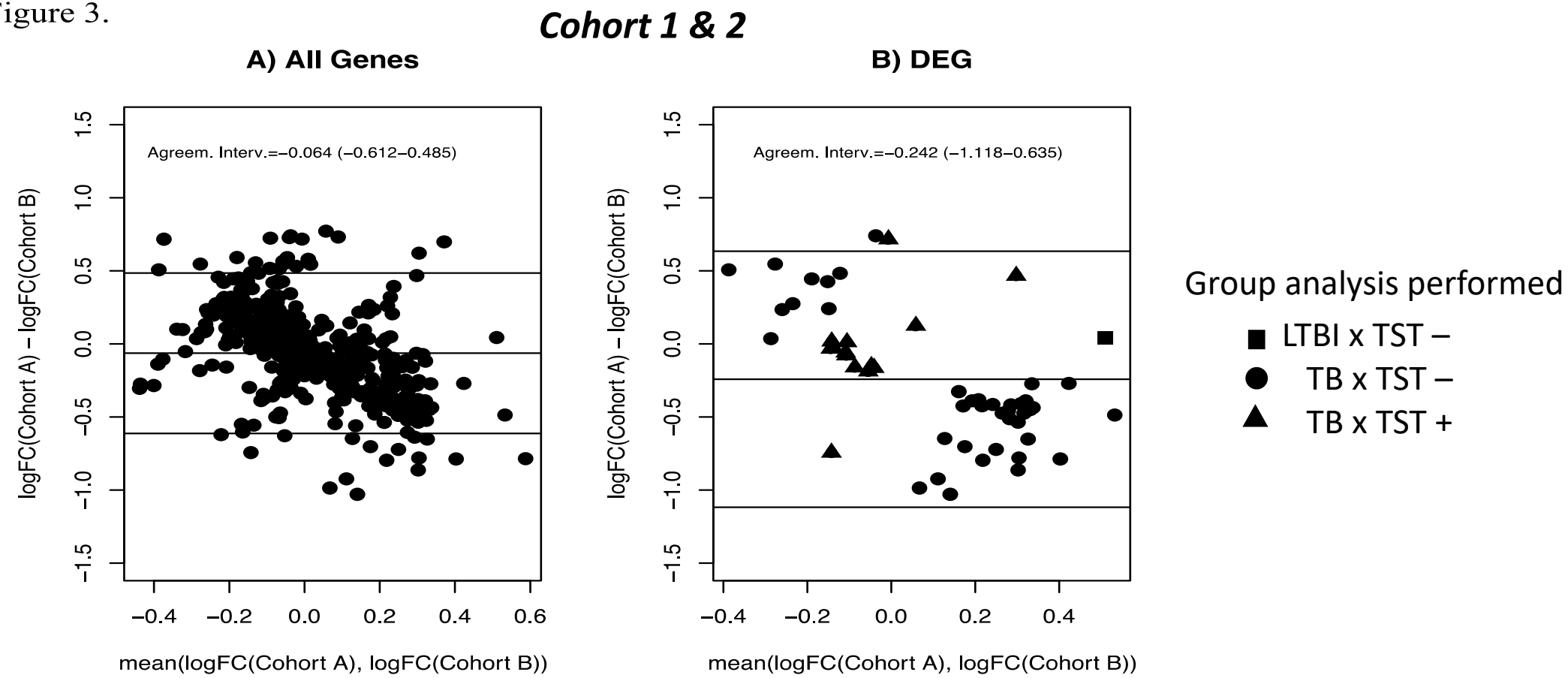


Fig3. Agreement/Concordance analysis between relative expression of genes on cohorts 1 and 2. A) Bland-Altman diagram displaying the mean agreement (-0.064), central horizontal line, and the 95% limits of agreement (-0.612 and 0.485), upper and lower horizontal lines, between log-fold changes (relative to the mean normalized expression of household contacts) of all 181 genes in the array (black circles) in cohorts 1 and 2; B) Bland-Altman diagram displaying the mean agreement (-0.242), central horizontal line, and the 95% limits of agreement (-1.118 and 0.635), upper and lower horizontal lines, between log-fold changes (relative to the mean normalized expression of household contacts) of differentially expressed genes (DEG) either in cohort 1 or 2; between LTBI (TST+) and HHC (TST-) (solid black squares), TB and HHC (TST-) (solid black circles), and TB and LTBI (TST+) (solid black triangles) contacts/patients.

Cohort 1

Figure 4.

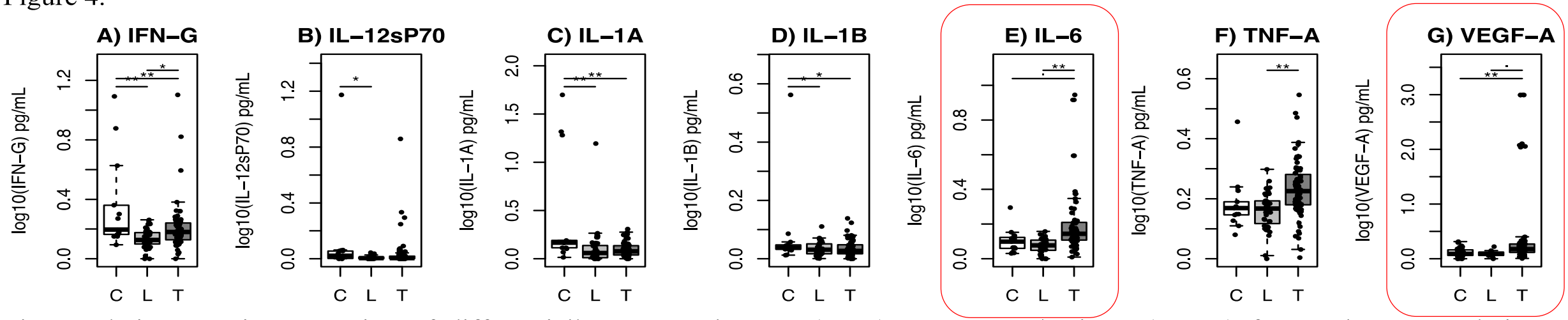


Fig4. Relative protein expression of differentially expressed genes (DEG) on contacts/patients (n=125) from cohort 1. Relative expression, represented by log-fold changes (relative to the mean normalized expression of household contacts (C)), of 7 DEG. C = household contacts (TST-) (white, n=13), L = latent tuberculosis (TST+) (lightgray, n= 38) infection patients, T = active tuberculosis patients (TB) (darkgray, n=73). Central bar indicates the median log-fold changes, while boxes boundaries indicate the interquartile range. Black dots represents each contact/patient in the subset of patients from cohort A. Statistical significance symbols: "." = p-value < 0.1, "*" = p-value <= 0.05, "**" = p-value <= 0.01.

Figure 5

Cohort 1

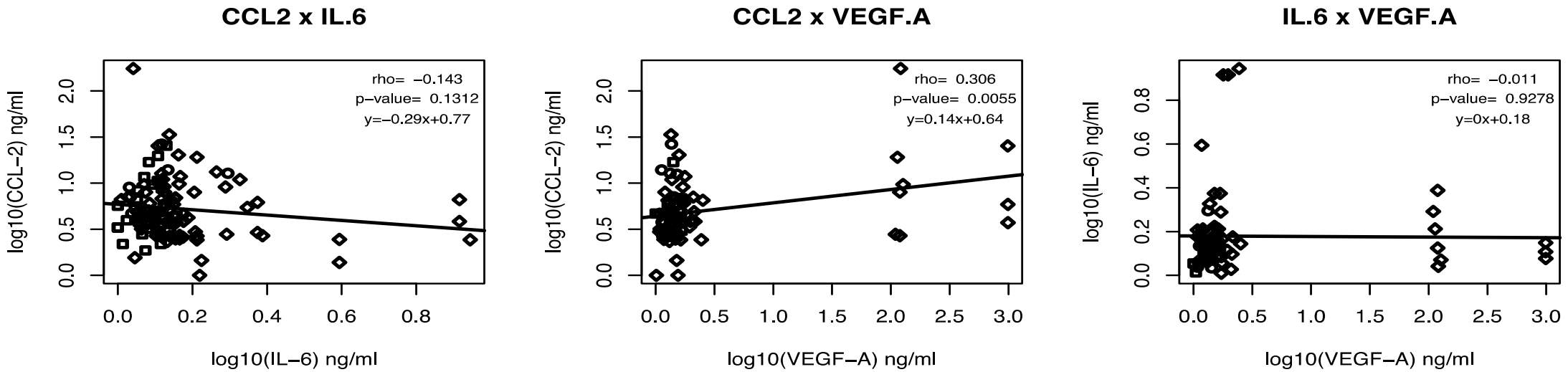
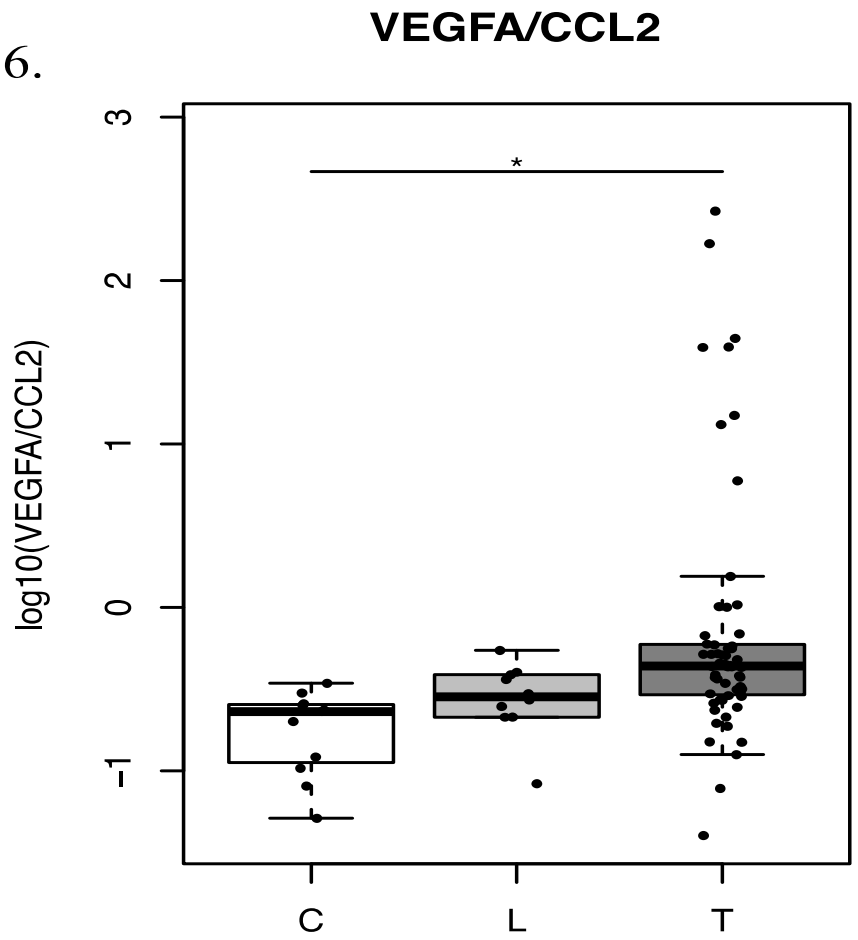


Fig5. Pairwise correlation between CCL2, IL-6 and VEGFa protein normalized expression values (logarithm (base 10)) on contacts/patients (n=195) from cohort A; TST- (empty black circles, n=58), TST+ (empty black squares, n=51), and TB (empty black lozenges, n=86) contacts/patients.

Figure 6.



Neurol Res. 2007 Dec;29(8):772-6.

Elevation of MCP-1 and MCP-1/VEGF ratio in cerebrospinal fluid of amyotrophic lateral sclerosis patients.

Nagata T[1], Nagano I, Shiote M, Narai H, Murakami T, Hayashi T, Shoji M, Abe K.

Author information

PLoS One. 2011 Feb 28;6(2):e16722. doi: 10.1371/journal.pone.0016722.

Cigarette smoke-related hydroquinone dysregulates MCP-1, VEGF and PEDF expression in retinal pigment epithelium in vitro and in vivo.

Pons M[1], Marin-Castaño ME.

Immune Function in Young Children With Previous Pulmonary or Miliary/Meningeal Tuberculosis and Impact of BCG Vaccination

Timothy R. Sterling, MD[a], Terezinha Martire, MD[b,c], Alexandre Silva de Almeida, PhD[b], Li Ding, MD[d], David E. Greenberg, MD[d], Lorena Alves Moreira, MS[b], Houda Elloumi, PhD[d], Angelica P. V. Torres, RN, BSN[b], Clemax Couto Sant'Anna, MD, PhD[e], Eliane Calazans, MD[f], Geraldo Paraguassu, MD[g,h], Tebeb Gebretsadik, MPH[i], Ayumi Shintani, PhD, MPH[i], Kathleen Miller, RN, BSN[a], Afranio Kritski, MD, PhD[b], Jose Roberto Lapa e Silva, MD, PhD[b], Steven M. Holland, MD[d]

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Abnormal Immune Responses in Persons with Previous Extrapulmonary Tuberculosis in an *In Vitro* Model That Simulates *In Vivo* Infection with *Mycobacterium tuberculosis*

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Fig 6. Ratio of normalized protein expression levels between VEGFa and CCL-2 genes on contacts/patients (n=195) from cohort A. C = household contacts (white, n=58), L = latent tuberculosis (lightgray, n=51) infection patients, T = active tuberculosis patients (darkgray, n=86). Central bar indicates the median log-fold changes, while boxes boundaries indicate the interquartile range. Black dots represents each contact/patient in the cohort A subset. Statistical significance symbols: "." = p-value < 0.1, "*" = p-value <= 0.05, "**" = p-value <= 0.01.

Conclusions

- Our evidences demonstrate that reanalysis of microarray data sets of human studies provided a potential approach to study Biomarkers in active tuberculosis.

- There is an increase in the VEGFA mRNA expression and protein synthesis detected in blood samples of active TB individuals

- There is a positive correlation and a positive ratio between VEGFA/CCL2 at protein levels suggesting a potential for the determination of active TB disease.

MCTI-CNPq/MS-SCTIE-DECIT-SVS-DST-Aids N º 30/2014 & ***FOA: PA-14-328***:
Administrative Supplements for U.S. - Brazil Biomedical Collaborative Research N º 30/2014

TITLE: **BIOMARKER DISCOVERY FOR TUBERCULOSIS INFECTION AND DISEASE**

Key persons in Brazil: José Roberto Lapa e Silva (PI), Afranio Lineu Kritski, Martha Maria de Oliveira, Milton Ozório Moraes, Valeria Rolla, Marcelo Ribeiro Alves, Eduardo Netto, Marcelo dos Santos Cordeiro, Alexandre Silva de Almeida

Key persons in the USA: Timothy R. Sterling, Catherine McGowan, Bryan Shepherd, Megan Turner, Amondrea Blackman, Cathy Jenkins, Spyros Kalamns, Chris Fiske

Two major sites

Vanderbilt
Division of Infectious Disease

UFRJ
Multidisciplinary laboratory of Reseach

Outline of Evaluation at Vandy-Rio study

Aim 1 - Identify Mtb-specific CD4+ T cells in 4 patient groups and measure activation/exhaustion markers.

Aim 2 - Assess Treg function in the different patient groups – this would expand on our previous paper where we found that people with EPTB have increased frequency of Treg and increased T cell activation (as measured by CD38 and HLA-DR)

Hospital Universitário Clementino Fraga Filho - UFRJ

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Cristina Fiske
Amondrea Blackman
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Catherine McGowan

Financial Suports:
Bolsa PNPD -CAPES/FAPERJ
Bolsa PosDoc Senior - FAPERJ
Pesquisa em Doenças Negligenciadas - CNPq
Projeto Equipamento Solidário – FAPERJ
NIH – CNPq FOA: PA-14-328

THANKS ABOVE ALL TO:

WHO/Jean Chung