**SUPPORTING INFORMATION**

**Bayesian Approach to Model CD137 Signaling in Human *M. tuberculosis* in vitro Responses**

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**ODE equations**

**APC cells dynamics**

Resting (uncommitted) APC (A0)



A0 activation in inflammatory context (macrophages)

A0 activation (inflammatory context independent) (DC)



A0 death

 (S1)

TNF- induced apoptosis of APC

Activated APC (Aa)

Aa death

 

 (S2)

Aa CD137 signaling by APC

Aa binding to

 blocking anti-CD137 mAb

Aa CD137 signaling by NK

Aa CD137 signaling by TL

CD137:CD137L

induced proliferation of APCa

Activated APC with CD137L signaling(As)

 

 (S3)



CD137:CD137L

induced death of APCa

TNF- induced

apoptosis of APC

As binding to

 blocking anti-CD137 mAb (mAb values are constant)

Activated APC with the receptor bound to blocking anti-CD137 mAb (AAb)

TNF- induced apoptosis of APC

AAb death

 

 (S4)

AAb CD137 signaling by APC

AAb CD137 signaling by NK

AAb CD137 signaling by TL

Activated APC, signalized by CD137::CD137L and with the receptor bound to blocking anti-CD137 mAb (As\_Ab)

 

 (S5)

TNF- induced

apoptosis of APC

CD137:CD137L

induced death of APCa

CD137:CD137L

induced proliferation of APCa

**NK cells dynamics**

Resting (uncommitted) NK (N0)

NK0 proliferation



NK0 death

N0 activation induced by the antigen, APC and IL-12

(S6)

 Activated NK (Na)



Na proliferation

(S7)

Na CD137L signaling by NK

Na CD137L signaling by APC

Na binding to

 blocking anti-CD137 mAb (mAb values are constant)

NK0 death

TNF- induced

apoptosis of APC

Activated NK with CD137L signaling (Ns)



NKs proliferation

 (S8)

Ns death

Ns binding to blocking anti-CD137 mAb

TNF- induced

apoptosis of APC



Activated NK with the receptor bound to blocking anti-CD137 mAb (NAb)





TNF- induced

apoptosis of APC

NKAb death

NKAb proliferation

**** (S9)

Activated NK, signalized by CD137::CD137L and with the receptor bound to blocking anti-CD137 mAb (Ns\_Ab)



TNF- induced

apoptosis of APC



NKs\_Ab proliferation

NKs\_Ab death

 (S10)

**TL cells dynamics**

Non-antigen-specific T cells (Tns)



Tns death

Tns proliferation

 (S11)

Naïve specific T cells (T0)

T differentiation (induced by activated APC)

T0 proliferation

T0 death



 (S12)

TNF- induced

apoptosis of APC

T cells activated by APC (with CD137:CD137L signaling) (Ts)

Ts death



 (S13)

Ts proliferation

T differentiation (induced by activated APC)

T cells activated by APC (without CD137:CD137L signaling) (Tbl)



TNF- induced

apoptosis of T cells

Effect of CD137 blockade in Ts death

 (S14)

Effect of CD137 blockade in Ts proliferation

T differentiation (induced by activated APC) with CD137::CD137L interaction blocked

**Media dynamics.**

*IFN- levels*





(S15)´´´

(S15)

(S15)´

(S15)´´

*TNF- levels*





(S16)´´´

(S16)

(S16)´´

(S16)´

Antigen concentration

 (Media treatment)

  (*M.tb* treatment and blocking treatment)

 (S17)

**Other APC equations**

Total number of APC

 (R1)

Percentage of APC producing IFN- and TNF-

**** (R2)

**** (R3)

Percentage of APC expressing receptor and ligand

 (R4)

**Other NK equations**

Total number of NK

 (R5)

Percentage of NK producing IFN- and TNF-

 (R6)

**** (R7)

Percentage of NK expressing receptor and ligand

 (R8)

**Other TL equations**

Total number of TL

 (R9)

Percentage of TL producing IFN- and TNF-

 (R11)

 (R12)

Percentage of TL expressing receptor

 (R10)

Percentage of TL undergoing apoptosis/necrosis

 (R13)

**Other Media equations.**

Total number of cells

 (R14)

Proliferation ratio

 (R15)

###  [tritiated thymidine](http://www.google.com.ar/url?sa=t&rct=j&q=triate+thymidine&source=web&cd=1&ved=0CCEQFjAA&url=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2F0027510769901146&ei=L0NFT4quL8KyiQL368m5Dg&usg=AFQjCNEmIeh8UrHSZP4nXVdW_d-oCzaI7Q&sig2=WPa8Q2RI2uaxH3ydcEOQFQ)incorporation

 (R16)

Time dependent variables are written in *italics*, parameters are written in normal type

Table S1. List of parameter names, descriptions, units and prior and posterior parameters distribution. Parameters distributions are presented in ranges.

|  |  |  |  |
| --- | --- | --- | --- |
| **Name** | **Reference** | **units** | **Description** |
| **rA** | [[1](#_ENREF_1)] | ------ | Ratio of APC in PBMC |
| **rN** | [[2](#_ENREF_2)] | ------ | Ratio of NKbright in PBMC |
| **rT** | [[2](#_ENREF_2)] | ------ | Ratio of TL PBMC |
| **rTsp** | [[3](#_ENREF_3)] [[4](#_ENREF_4)] | ------ | Ratio of TLspecific to M.tb |
| **A0** | Estimated | ng A0-1 h-1 | IFN production by A0 |
| **Aa** | Estimated | ng Aa-1 h-1 | IFN production by Aa |
| **IA** | [[5](#_ENREF_5),[6](#_ENREF_6)] | ------ | Induction factor of IFN production by CD137::CD137L of APC |
| **A0** | [[7](#_ENREF_7)] | ng Aa-1 h-1 | TNFproduction by A0 |
| **Aa** | [[7](#_ENREF_7)] | ng Aa-1 h-1 | TNF production by Aa |
| **IA** | [[5](#_ENREF_5),[6](#_ENREF_6)] | ------ | Induction of TNFproduction by CD137::CD137L of APC |
| **μA0** | [[7](#_ENREF_7)] | h-1 | Death rate for A0 |
| **μAa** | [[7](#_ENREF_7)] | h-1 | Death rate for Aa |
| **μIA** | [[8](#_ENREF_8)] [[9](#_ENREF_9)] | ------ | Induction of death by CD137::CD137L of APC |
| **μαA** | [[10](#_ENREF_10)] | h-1 | Maximum rate of TNF- dependent apoptosis of APC |
| **KαμA** | [[7](#_ENREF_7)] | ng | Half-sat for TNF-dependent apoptosis of APC |
| **A** | [[9](#_ENREF_9),[11](#_ENREF_11)] | h-1 | Proliferation rate of As |
| **rA0** | Estimated | ------ | A0IFN+/A0 ratio  |
| **rAa** | Estimated | ------ | AaIFN+/Aa ratio  |
| **rA0** | Estimated | ------ | AaTNF+/Aa ratio |
| **rRLA0** | Estimated | ------ | A0 CD137+ CD137L+ / A0 ratio |
| **k(AxA)** | [[7](#_ENREF_7)] | cell-1 h-1 | APC-APC interaction rate |
| **k(AxN)** | Estimated | cell-1 h-1 | APC-NK interaction rate |
| **k(AxT)** | [[7](#_ENREF_7)] | cell-1 h-1 | APC-LT interaction rate |
| **k(AxAg)** | [[7](#_ENREF_7)] | μg-1 h-1 | APC activation rate  |
| **k(AxAg)** | [[7](#_ENREF_7)] | μg-1 h-1 | APC-APC interaction rate (inflammatory context) |
| **k(AxAb)**  | Estimated | μg-1 h-1 | Ab binding rate for APC |
| **KA0,Aa)** | Estimated | μg-1 | Half-sat of IFN- on APC activation |
| **K(A0,Aa)** | Estimated | μg-1 | Half-sat of TNF- on APC activation |
| **N0** | [[10](#_ENREF_10)] | ng-1 h-1 | IFN production by N0 |
| **Na** | [[10](#_ENREF_10)] | ng-1 h-1 | IFN production by Na |
| **IN** | [[12](#_ENREF_12)] |  | Induction of IFN production by CD137 of NK |
| **N0** | Estimated | μg-1 h-1 | TNF production by N0 |
| **Na** | [[13](#_ENREF_13)] | μg-1 h-1 | TNF production by Na |
| **IN** | Estimated | ------ | Induction of TNF production by CD137 of NK |
| **μN0** | [[14](#_ENREF_14)] | h-1 | Death rate for N0 |
| **μNa** | [[14](#_ENREF_14)] | h-1 | Death rate for Na |
| **μαN** | Estimated | h-1 | Maximum rate of TNF- dependent apoptosis of NK |
| **KμN** | Estimated | ng | TNF half-sat for TNF- dependent apoptosis of NK |
| **N0** | [[14](#_ENREF_14)] | h-1 | N0 Maximum proliferation rate  |
| **Na** | [[14](#_ENREF_14)] | h-1 | Na Maximum proliferation rate |
| **rN0** | [[15](#_ENREF_15)] | ------ | Na IFN-+/Na ratio |
| **rN0** | [[16](#_ENREF_16)] | ------ | N0 TNF-+/N0 ratio |
| **rNa** | Estimated | ------ | Na TNF-+/Na ratio |
| **rRLN0** | [[12](#_ENREF_12)]  | ------ | N0 CD137+ CD137L+/N0 ratio |
| **rRLNa** | [[12](#_ENREF_12)] | ------ | Na CD137+ CD137L+/Na ratio |
| **k(NxN)** | Estimated | cell-1 h-1 | NK-NK interaction rate |
| **k(NxAb)** | Estimated | μg-1 h-1 | Ab binding rate for NK |
| **k(N0,Na)A** | Estimated | μg-1 cell-1 | Maximum NK activation rate, dependent on APC and indirect IL-12 |
| **KA(N0,Na)** | Estimated | μgcell | APC half-sat on enhancement of NK activation |
| **K(N0,Na)** | Estimated | ng | Half-sat of IFN- on NK activation |
| **K(N0,Na)** | Estimated | ng | Half-sat of TNF- on NK activation |
| **T0** | [[17](#_ENREF_17)] | ng-1 h-1 | IFN-production rate by LT0 |
| **Ts** | [[10](#_ENREF_10)] | ng-1 h-1 | IFN-production rate by LTs |
| **IT** | [[18](#_ENREF_18)] [[19](#_ENREF_19)] | ------ | Induction of IFN-production by CD137 |
| **T0** | Estimated | ng-1 h-1 | TNF-production rate by T0 |
| **Ts** | [[10](#_ENREF_10)] [[20](#_ENREF_20)] [[21](#_ENREF_21)] | ng-1 h-1 | TNF-production rate by Ts |
| **IT** | [[19](#_ENREF_19)] | ------ | Induction of TNF-production by CD137 |
| **μT0** | [[14](#_ENREF_14)] [[7](#_ENREF_7)] | h-1 | Apoptosis rate of T0 |
| **μTs** | [[7](#_ENREF_7)] | h-1 | Apoptosis rate of Ts |
| **μIT** | [[22](#_ENREF_22)] | ------ | Induction of apoptosis rate by CD137 |
| **μαT** | [[7](#_ENREF_7)] | h-1 | Maximum rate of TNF-dependent apoptosis of TL |
| **KT** | [[7](#_ENREF_7)] | ng | TNF half-sat for TNF-dependent apoptosis of TL |
| **T0** | [[14](#_ENREF_14)] | h-1 | Proliferation rate of T0 |
| **Ts** | [[7](#_ENREF_7)] | h-1 | Proliferation rate of Ts |
| **IT** | [[22](#_ENREF_22)] | ------ | Induction of proliferation rate by CD137 |
| **rT0** | [[23](#_ENREF_23)] | ------ | T0 IFN-+/T0 ratio |
| **rTs** | UD\* | ------ | Ts IFN-+/Ts ratio |
| **rT0** | Estimated | ------ | T0 TNF-+/T0 ratio |
| **rTs** | UD\* | ------ | Ts TNF-+/Ts ratio |
| **rRT0** | [[22](#_ENREF_22)] | ------ | T0CD137+/T0 ratio |
| **K(TxAb)** | Estimated | μg-1 h-1 | TL-mAb binding rate |
| **Ap** | [[24](#_ENREF_24)] | h | Duration of Apoptosis |
| **μ** |  | h-1 | Degradation rate of TNF- |
| **μ** | [[25](#_ENREF_25)] [[26](#_ENREF_26)] | h-1 | Degradation rate of IFN- |
| **μAg** |  | h-1 | Degradation/internalization rate of Ag |
| ****Tym** | Estimated | cpm cell-1 | Scaling factor [H3]timidine-proliferation |
| **mCells** | Estimated | cell | Maximum number of cell supported by the media |

\*UD=Unpublished data

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