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Supplementary Table 2. Host-directed therapeutics for tuberculosis.

Major target	General mechanism	TB specific effect	Developmental stage as HDT for TB	Licensed/clinical development	Ref
Small molecules (repurposed)					
Autophagy					
Metformin	Inhibition of mitochondrial respiratory chain, modulation of protein kinases	Improved killing of Mtb via ROI, phagolysosome fusion, autophagy	Preclinical	Diabetes (licensed)	1
Carbamazepine	Sodium channel modulator	Mtb killing through autophagy	Preclinical	Anti-convulsant (licensed)	2
Valproic acid	Sodium channel and histone deacetylase modulator	Mtb killing through autophagy	Preclinical	Anti-convulsant (licensed)	2
Statins	HMG-CoA reductase inhibitor	Intracellular killing of Mtb through increased phagolysosome fusion and autophagy ?	Preclinical	Lipid reducers (licensed)	3-6
Fluoxetine	Selective serotonin reuptake inhibitor	Mtb killing through autophagy	Preclinical	Antidepressant (licensed)	7
Verapamil	Calcium channel blocker	Mtb killing through autophagy	Preclinical	Anti-arrhythmic (licensed)	8-10
Arachidonic acid pathway					
Zileuton	5-lipoxygenase inhibitor	Antimycobacterial activity through modulation of IL-1-PGE2-IFN I network	Preclinical	Asthma (licensed)	11

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Ibuprofen / Diclofenac	COX inhibitor reducing PGE2 synthesis	Ameliorated inflammation and pathology	Clinical	Pain, fever (licensed)	12-14
Acetylsalicylic acid (Aspirin)	COX inhibitor reducing PGE2 synthesis	Ameliorated inflammation and pathology	Clinical	Pain, fever (licensed)	15-17
Glucocorticoids					
Prednison / Dexamethasone	Broad anti-inflammatory effects	Ameliorated / Exacerbated inflammation and pathology	Clinical	Anti-inflammatory (licensed)	18-22
Kinase inhibitors					
Imatinib	Tyrosine kinase ABL-inhibitor	Inhibition of Mtb engulfment and stimulation of phagosome acidification	Preclinical	Leukemia (licensed)	23-25
Gefitinib	Tyrosine kinase inhibitor blocking EGFR	Antimycobacterial activity and stimulation of autophagy	Preclinical	Cancer (licensed)	7
TNF-α					
Cilostazol	Phosphodiesterase 3 inhibitor	Intracellular killing of Mtb through TFN-α modulation	Preclinical	Claudication (licensed)	26
Sildenafil	Phosphodiesterase 5 inhibitor	Synergy with Cilostazol	Preclinical	Erectile dysfunction (licensed)	26
Thalidomide derivates	Phosphodiesterase 4 inhibitor	Intracellular killing of Mtb through TFN-α modulation	Clinical	Leprosy, cancer (licensed)	27-31
Pentoxifylline	Phosphodiesterase inhibitor	Intracellular killing of Mtb through TFN-α modulation	Preclinical	Claudication (licensed)	32,33
Desipramine	Acid sphingomyelinase inhibitor	Diminishes excessive TNF-α mediated tissue damage	Preclinical	Antidepressant (licensed)	34
Alisporivir	Cyclophilin D inhibitor	Diminishes excessive TNF-α mediated tissue damage	Preclinical	Hepatitis C (late stage clinical trial)	34

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Antibiotics					
TB drugs: Isoniazid, Pyrazinamide	TB, chemotherapy	Autophagy of Mtb infected macrophages	Preclinical	TB drugs (licensed)	35,36
Nitazoxanide	Antiparasitic drug with anti Mtb activity	Autophagy	Preclinical	Antiparasitic drug (licensed)	37
Doxycycline	Antibiotic	Inhibitor matrixmettalloproteases	Preclinical	Antibiotic (licensed)	38
Nutraceutical and derivatives					
Vitamin D 3 / Phenylbutyrate	Macrophage activation and antimicrobial peptide induction / Histone acetylase inhibitor	Intracellular killing of Mtb by stimulating cathelicidin (combination with vitamin D)	Clinical	Dietary supplement / Urea cycle disorder (licensed)	39-48
Vitamin A / All-trans-retinoic acid (ATRA)	Antimicrobial and macrophage activation / Modulation of cell proliferation and differentiation	(Intracellular) Killing of Mtb / Block of MDSC resulting in improved antimycobacterial immunity	Clinical / Preclinical	Dietary supplement / Acne, cancer (licensed)	49-55
Cytokine					
Interferon-γ	Macrophage activation	Intracellular killing of Mtb	Clinical	CGD/Osteopetrosis (licensed)	56-59
Anti-cytokine					
Adalimumab, Infliximab (anti-TNF-α mAb)	Blocking of TNF-α to reduce excessive inflammation	Diminishes excessive TNF-α mediated tissue damage / Lesion destabilization	Clinical	Rheumatoid arthritis (licensed)	60-62
Etanercept (soluble TNF-α receptor)	Blocking of TNF-α to reduce excessive inflammation	Diminishes excessive TNF-α mediated necrosis thereby increasing intracellular Mtb killing	Clinical	Rheumatoid arthritis (licensed)	19

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Siltuximab (anti-IL-6 mAb)	Blocking of IL-6 to reduce excessive inflammation	Ameliorated inflammation and pathology through IL-6 reduction notably in IRIS	Preclinical	Castleman disease (licensed)	63
Tocilizumab (anti-IL-6R mAb)	Blocking of IL-6 to reduce excessive inflammation	Ameliorated inflammation and pathology through IL-6 reduction notably in IRIS	Preclinical	Rheumatoid arthritis (licensed)	63
Checkpoint control					
Ipilimumab (anti-CTL4 mAb)	Release from CTL-4 (primarily CD8 T cells) mediated checkpoint control	Improved T cell immunity	Preclinical	Cancer (licensed)	64-66
Nivolumab, Pembrolizumab (anti-PD-1 mAb)	Release from PD-1 (primarily CD4 T cells) mediated checkpoint control	Improved T cell immunity	Preclinical	Cancer (licensed)	67-71
Anti-Tim3, mAb	Release from Tim3 mediated checkpoint control	Improved antimycobacterial immunity	Preclinical	Cancer (preclinical)	72-74
Angiogenesis inhibitor					
Bevacizumab (anti VEGF mAb)	Angiogenesis inhibitor	Angiogenesis inhibition resulting in improved antimycobacterial activity	Preclinical	Cancer (licensed)	75-79
Pazopanib	Tyrosine kinase inhibitor affecting angiogenesis by blocking VEGF	Angiogenesis inhibition resulting in antimycobacterial activity	Preclinical	Cancer (licensed)	77
Cell therapy					
Mesenchymal stroma cells (MSC)	Diminish excessive inflammation	T-cell reconstitution	Clinical	Hyper-inflammation (clinical trial)	80,81

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