

Passage of known and proposed targets in the targetTB pipeline

An account of the passage of known targets (previously reported in literature) through the targetTB pipeline. The putative targets are classified based on their broad functional categories. A, B, C, E, F, G, H, I, J and K refer to the different filters depicted in Fig. 1 and described in the text. ‘✓’ indicates that the given protein passes the filter, while a ‘✗’ indicates a failure. A ‘?’ indicates that the analysis was not performed due to lack of appropriate data, while ‘-’ indicates that the protein was not passed through the filter due to failure at a previous stage. All proteins in the H-list indicated in Fig. 3 would have a ‘✓’ at levels A–H. ‘●’ indicates the additional lists (I/J/K) in which a target from the H-List is present.

Target	Remarks	targetTB pipeline										
		A	B	C	E	F	G	H	I	J	K	
I. Cell Wall Biosynthesis												
DdlA (Rv2981c)	Known target of cycloserine [1]	✓	✓	✗	✓	✓	✓	✗				
FtsZ (Rv2150c)	Suggested as possible drug target [2, 3]	✓	✓	✓	✓	✓	✗	✗				
<i>Arabinogalactan biosynthesis</i>												
EmbA (Rv3794)	Known target for ethambutol [4, 5]	✓	✓	✓	✓	✓	✓	✓				✓
EmbB (Rv3795)	-do-	✓	✓	?	✓	✓	✓	✗				✗
EmbC (Rv3793)	-do-	✓	✓	✓	✓	✓	✓	✓				✓
GlFT1 (Rv3782)	Suggested as possible target [6, 7]	✓	✓	✓	✓	✓	✓	✓				✓
GlFT2 (Rv3808c)	Suggested as important target for the development of new anti-tuberculosis drugs [8]; suggested as possible target [6, 7]	✓	✓	✓	✓	✓	✓	✓				✓
GlF (Rv3809c)	Suggested as important target for the development of new anti-tuberculosis drugs [8]	✓	✓	✓	✓	✗	✗	✗				✗
<i>Peptidoglycan biosynthesis</i>												
AftA (Rv3792)	Suggested as an attractive target [9]	✓	✓	✗	✓	✓	✓	✗				✗
AftB (Rv3805c)	Suggested as a potential target [10]	✓	✓	✓	✓	✓	✓	✓				✓
MurG (Rv2153c)	Suggested as a potential target [11]	✓	✓	✓	✓	✓	✓	✓				✓
MurX (Rv2156c)	-do-	✓	✓	✓	✓	✓	✓	✓				●
RmlA (Rv0334)	Important in synthesis of dTDP-rhamnose [12]	✓	✓	✗	✗	✗	✗	✗				●
RmlB (Rv3464)	Suggested as potential target [12]	✓	✗	-	✓	✗	✗	✗				●
RmlC (Rv3465)	Suggested as potential target [12]	✓	✓	✓	✓	✓	✓	✓				●
RmlD (Rv3266c)	Important in synthesis of dTDP-rhamnose [12]	✓	✓	✓	✓	✓	✓	✓				●
Wag31 (Rv2145c)	Identified as novel target [13]	✓	✓	✓	✓	✓	✓	✓				●
II. Lipid Metabolism												
<i>Mycolic acid biosynthesis</i>												
FabH (Rv0533c)	Possible target of thiolactomycin; also suggested as potential target [14, 15]	✓	✓	✓	✓	✓	✓	✓				●
FabD (Rv2243)	Suggested as a potential target [16–18]	✓	✓	✓	✓	✓	✓	✓				●
AcpM (Rv2244)	Induced on isoniazid treatment [16, 19]	✓	✓	✓	✓	✓	✓	✓				●
Pks13 (Rv3800c)	Suggested as a promising target against <i>Corynebacterineae</i> [20]	✓	✓	✓	✓	✓	✓	✓				●
InhA (Rv1484)	Known target for isoniazid, ethionamide [21]	✓	✓	✓	✓	✓	✓	✓				●
MabA (Rv1483)	Recommended as a possible rational target [22, 23]	✗	✗	-	✓	✓	✓	✗				●
KasA (Rv2245)	Possible target of thiolactomycin [24]/isoniazid [25]	✓	✗	-	✓	✓	✓	✗				●
KasB (Rv2246)	Possible target of thiolactomycin [24]	✓	✗	-	✓	✓	✓	✗				●
PcaA (Rv0470c)	Suggested as a possible target of thiacetazone [26]	✓	✓	✓	✓	✓	✓	✓				●
CmaA2 (Rv0503c)	-do-	✓	✓	✓	✓	✓	✓	✓				●
MmaA1 (Rv0645c)	-do-	✓	✓	✓	✓	✓	✓	✓				●
MmaA2 (Rv0644c)	-do-	✓	✓	✓	✓	✓	✓	✓				●
MmaA3 (Rv0643c)	-do-	✓	✓	✓	✓	✓	✓	✓				●
MmaA4 (Rv0642c)	Suggested as a possible target of thiacetazone [26]; suggested as a possible target [27]	✓	✓	✓	✓	✓	✓	✓				●
FadD32 (Rv3801c)	Suggested as a promising target [28]	✓	✓	✓	✓	✓	✓	✓				●
AccD4 (Rv3799c)	Suggested as a promising target [28]	✓	✗	-	✓	✓	✓	✗				●
AccA3 (Rv3285)	Suggested as a possible target [29]	✓	✗	-	✓	✓	✓	✗				●
AccD5 (Rv3280)	Suggested as a possible target [29]	✓	✗	-	✓	✗	✗	✗				●
AccE5 (Rv3281)	Suggested as a possible target [29]	✓	✓	?	✓	✓	✓	✗				●
DesA3 (Rv3229c)	Suggested as a possible target [30]	✓	✓	?	✓	✓	✓	✗				●
Fas (Rv2524c)	Possible target of pyrazinamide [31]	✓	✓	✓	✓	✓	✓	✓				●
III. Intermediary Metabolism and Respiration												
AdoK (Rv2202c)	Suggested as a good bioactivator/pro-drug target [32]; suggested as potential drug target [33]	✓	✓	✓	✓	✓	✓	✓				●
(Rv1347c)	Suggested as a valid drug target [34]	✓	✓	✗	✓	✓	✓	✗				●
Dxr (Rv2870c)	Suggested as a highly promising drug target [35]	✓	✓	✗	✓	✓	✓	✗				●
HadA (Rv0635)	HadAB is an exciting target [36]	✓	✓	✓	✓	✓	✓	✓				●
HadB (Rv0636)	HadAB, HadBC are exciting targets [36]; likely target of dehydratase inhibitors in <i>M. bovis</i> [37, 38]	✓	✓	✓	✓	✓	✓	✓				●
HadC (Rv0637)	HadBC is an exciting target [36]	✗	✓	-	✓	✓	✓	✗				●

Target	Remarks	targetTB					pipeline					
		A	B	C	E	F	G	H	I	J	K	
HisE (Rv2122c)	Suggested as potential drug target [39]	✓	✓	✓	✓	✗	✗	✗	✗	✗		
Nat (Rv3566c)	Inhibition of Nat contributes to anti-mycobacterial activity of <i>Warburgia salutaris</i> [40]	✓	✓	✓	✓	✓	✓	✓	✓	✓		
ThyX (Rv2754c)	Suggested as potential target in several organisms [41]	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Tmk (Rv3247c)	Suggested as potential drug target [42,43]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	
Tpi (Rv1438)	Suggest the design of drug exploiting difference with the host enzyme [44]	✓	✗	–	✓	✓	✓	✓	✗	✗		
<i>Nucleotide biosynthesis</i>												
GuaB1 (Rv1843c)	Suggested as a drug target in several organisms [45]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	●
GuaB2 (Rv3411c)	–do–	✓	✓	✗	✓	✓	✓	✓	✗	✗		
GuaB3 (Rv3410c)	–do–	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	
RelA (Rv2583c)	Important in the survival of <i>Mtb</i> during nutrient starvation [46,47]	✗	✓	–	✓	✓	✗	✗	✗	✗		
<i>Amino acid biosynthesis</i>												
Ald (Rv2780)	Suggested as potential drug target [48]	✓	✓	✗	✓	✓	✓	✓	✗	✗		
Asd (Rv3708c)	Suggested as an attractive drug target [49]	✓	✓	✓	✓	✓	✗	✗	✗	✗		
DapA (Rv2753c)	Stated as an important drug target [50]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	
DapC (Rv0858c)	Enzymes of lysine biosynthesis pathway are potential target candidates [51]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	
GlnA1 (Rv2220)	Essential for <i>Mtb</i> virulence [52]	✓	✓	✗	✓	✓	✗	✗	✗	✗		
LysA (Rv1293)	Lysine auxotroph has vaccine potential [53]; suggested as potential target [54]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	
LeuD (Rv2987c)	Δ leuD mutant unable to replicate in macrophages <i>in vitro</i> [55]	✓	✓	✓	✗	✗	✗	✗	✗	✗		
ProC (Rv0500)	Essential for <i>Mtb</i> virulence [56]	✓	✗	–	✓	✓	✓	✓	✗	✗		
TrpD (Rv2192c)	–do–	✓	✓	✓	✗	✓	✓	✓	✗	✗		
LeuA (Rv3710)	Suggested as potential target [57]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	
DapB (Rv2773c)	Suggested as potential target [58]	✓	✓	✓	✗	✗	✗	✗	✗	✗		
AroA (Rv3227)	Genes of the shikimate pathway suggested as potential targets [59–61]	✓	✓	✓	✗	✗	✗	✗	✗	✗		
AroB (Rv2538c)	Shikimate pathway suggested as an attractive target [62]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	●
AroE (Rv2552c)	Suggested as a potential target [63]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	
AroF (Rv2540c)	Suggested as a potential target [64]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	
AroG (Rv2178c)	Genes of the shikimate pathway suggested as potential targets [59,65]	✓	✓	✓	✓	✓	✓	✓	✓	✓		
AroK (Rv2539c)	Genes of the shikimate pathway suggested as potential targets [59,60]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	
AroQ (Rv0948c)	Suggested as a promising target [66]	✗	✓	–	✓	✓	✓	✓	✗	✗		
*AroQ (Rv1885c)	Suggested as a novel target [67]; suggested as a promising target [66]	✓	✓	✓	✓	✓	✓	✓	✓	✓		
FbpB (Rv1886c)	Important promoter region for AroQ [66]	✓	✓	✓	✓	✓	✓	✓	✓	✓		
ArgA (Rv2747)	Essential enzyme catalysing initial step of arginine biosynthesis [68]	✓	✓	✓	✓	✓	✓	✓	✓	✓		
ArgC (Rv1652)	Suggested as potential target [69]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	●
AlrA (Rv3423c)	Known target of Cycloserine [1]	✓	✓	✗	✓	✓	✓	✓	✗	✗		
<i>Cofactor biosynthesis</i>												
DfrA (Rv2763c)	Important drug target in many pathogens [70]. Suggested as drug target in [70,71]	✓	✗	–	✓	✓	✓	✓	✗	✗		
PanB (Rv2225)	Critical for pantothenic acid synthesis [72]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	●
PanC (Rv3602c)	Critical for pantothenic acid synthesis [72]; suggested as potential target [73]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	●
PanD (Rv3601c)	Critical for pantothenic acid synthesis [72]; suggested as potential target [74]	✓	✓	✗	✓	✓	✓	✓	✗	✗		
PanK (Rv1092c)	Prokaryotic enzymes involved in the synthesis of CoA are good targets [75]; [76]	✓	✓	✓	✓	✓	✓	✓	✓	✓		
/CoaA												
Dfp (Rv1391)	Prokaryotic enzymes involved in the synthesis of CoA are good targets [75]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	●
/CoaBC												
RibC (Rv1412)	Promising target [77,78]; inhibition of enzymes involved in riboflavin biosynthesis provides a rational strategy for antibiotic drug design [79]	✓	✓	✓	✗	✓	✓	✓	✗	✗		
RibH (Rv1416)	–do–	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	●
<i>Mycothioliol biosynthesis</i>												
MshA (Rv0486)	Essential for production of GlcNAc-Ins and growth in <i>Mtb</i> [80]; enzymes involved in mycothioliol biosynthesis suggested as potential targets [81–84]	✗	✓	–	✓	✓	✓	✓	✗	✗		
MshB (Rv1170)	Important enzyme in mycothioliol biosynthesis [85]; mycothioliol biosynthetic pathway could constitute novel and important drug targets [83]; proposed as target [86]	✓	✓	✓	✓	✓	✓	✓	✓	✓		
MshC (Rv2130c)	Required for mycothioliol production and is essential for <i>Mtb</i> survival [81]; Enzymes involved in mycothioliol biosynthesis suggested as potential targets [81–84]	✓	✗	–	✓	✓	✓	✓	✗	✗		
MshD (Rv0819)	Enzymes involved in mycothioliol biosynthesis suggested as potential targets [81–84]; survival of <i>Mtb</i> MshD mutants is severely compromised in activated and non-activated macrophages [87]	✓	✓	✓	✓	✓	✓	✓	✓	✓		
<i>Sulphur Metabolism</i>												
CysH (Rv2392)	Catalyses the first committed step in the biosynthesis of reduced sulphur compounds. CysH is actively expressed during the dormant phase of <i>Mtb</i> and in the environment of macrophages [88,89]. Humans do not reduce sulfate for <i>de novo</i> cysteine biosynthesis and therefore do not have a CysH equivalent; hence can be an attractive drug target [90–93]; CysH is important for <i>Mtb</i> protein during latent infection [94]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	
Mca (Rv1082)	Critical role in mycobacterial detoxification of antibiotics [95]	✗	✓	–	✓	✓	✓	✓	✗	✗		
<i>Sulphate assimilation enzymes</i>												
CysT (Rv2399c)	Attractive targets, as many of these have no homologues in humans [90]	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	●
CysW (Rv2398c)	–do–	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	●
CysA (Rv2397c)	–do–	✓	✗	–	✗	✗	✗	✗	✗	✗		
SubI (Rv2400c)	–do–	✓	✓	✗	✓	✓	✓	✓	✗	✗		
CysN (Rv1286)	–do–	✓	✓	✗	✓	✓	✓	✓	✗	✗		
CysD (Rv1285)	–do–	✓	✓	✓	✓	✓	✓	✓	✓	✓	●	

Target	Remarks	targetTB pipeline									
		A	B	C	E	F	G	H	I	J	K
CysC (Rv1286)	-do-	✓	✓	✗	✓	✓	✓	✗			
NirA (Rv2391)	-do-	✓	✓	✓	✓	✓	✓	✓	●		
CysK (Rv2334)	-do-	✗	✗	-	✓	✓	✗	✗			
CysM (Rv1336)	-do-	✗	✓	-	✓	✓	✓	✗			
CysM3 (Rv0848)	-do-	✓	✓	✓	✓	✓	✓	✓	●	●	
<i>Terpenoid biosynthesis</i>											
IspD (Rv3582c)	Potential drug target [96]	✓	✓	✓	✓	✓	✓	✓	●	●	
IspE (Rv1011)	-do-	✓	✓	✓	✓	✓	✓	✓		●	
IspF (Rv3581c)	Potential drug target [96]; attractive target in many pathogens [97]	✓	✓	✓	✓	✓	✓	✓	●	●	
<i>Glyoxylate shunt</i>											
Icl (Rv0467)	Required for persistence of <i>Mtb</i> in macrophages and mice [98]; suggested as an attractive target [99]. Icl1 and Icl2 are required for fatty acid catabolism and virulence in <i>Mtb</i> [100]	✓	✓	✓	✓	✓	✗	✗			
AceAB (Rv1916)		✗	✓	-	✓	✓	✓	✗			
CitE (Rv2498c)	May be useful as drug target [101]	✗	✗	-	✓	✓	✓	✗			
<i>ATP Synthesis</i>											
AtpE1 (Rv1305)	Inhibited by a diarylquinoline drug R207910 <i>in vitro</i> [102]	✓	✓	✓	✓	✓	✓	✓			
<i>Menaquinone Biosynthesis</i>											
MenA (Rv0534c)	Possibly an essential nutrient for <i>Mtb</i> [103]	✓	✓	?	✓	✓	✓	✗			
MenB (Rv0548c)	-do-	✓	✓	✓	✓	✓	✗	✗			
MenC (Rv0553)	-do-	✓	✓	✓	✓	✓	✓	✓			
MenD (Rv0555)	-do-	✓	✓	✓	✓	✓	✓	✓			
MenE (Rv0542c)	-do-	✓	✓	✓	✓	✓	✓	✓	●	●	
MenH (Rv0558)	-do-	✓	✓	✓	✓	✓	✓	✓		●	
<i>Cytochrome P450s</i>											
Cyp121 (Rv2276)	Putative essential gene. Possible role in virulence through studies with Δ AraC/XylS gene regulator mutant (Δ Rv1931c) [104]. Induced in isoniazid- and thiolactomycin-treated <i>Mtb</i> [105]	✓	✓	✓	✓	✓	✓	✓		●	
Cyp125 (Rv3545c)	Induced in macrophages. Essential for infection in mice [106]	✗	✓	-	✓	✓	✓	✗			
Cyp128 (Rv2268c)	Possible essential gene. Required for <i>Mtb</i> growth <i>in vitro</i> . Expression upregulated post-starvation [104]	✓	✓	✓	✓	✗	✓	✗			
Cyp130 (Rv1256c)	Absent from <i>M. bovis</i> BCG vaccine strain (deletion RD13) [104]	✗	✓	-	✓	✓	✓	✗			
Cyp132 (Rv1394c)	Possible role in <i>Mtb</i> virulence. Transcription controlled by adjacent AraC transcriptional regulator [104,107]	✓	✓	✓	✓	✗	✓	✗			
Cyp141 (Rv3121)	Absent from <i>M. bovis</i> BCG vaccine strain (deletion RD12) [104]	✗	✓	-	✓	✓	✓	✗			
Cyp144 (Rv1777)	Possible role in virulence [104]	✓	✓	✗	✗	✗	✓	✗			
IV. Information Pathways											
<i>DNA Synthesis</i>											
NrdB (Rv0233)	Ribonucleotide reductases (RNRs) are attractive targets for anti-proliferative drugs [108] and subunit vaccines [109] in other organisms [110]	✗	✓	-	✓	✓	✓	✗			
NrdE (Rv3051c)	<i>Mtb</i> RNR is a potential drug target; inhibition of RNR in a variety of mycobacterial species substantially alters the growth patterns of the organisms [111]; suggested as potential target [112] [110]	✓	✓	✗	✓	✓	✗	✗			
NrdF1 (Rv1981c)	[110]	✓	✓	✓	✓	✗	✗	✗			
NrdF2 (Rv3048c)	Potential target [112] [110]	✓	✓	✓	✓	✗	✗	✗			
LigA (Rv3014c)	Stated as a novel, validated and attractive drug target [113–115]; suggested as a possible drug target [116]	✓	✓	✓	✗	✓	✓	✗			
GyrA (Rv0006)	Known target of fluoroquinolones [117,118]	✗	✓	-	✓	✓	✗	✗			
GyrB (Rv0005)	-do-	✓	✓	✗	✓	✓	✗	✗			
RpoB (Rv0667)	Known target of rifampicin [119]	✓	✓	✓	✓	✗	✗	✗			
RpsL (Rv0683)	Known target of Streptomycin [120]	✓	✗	-	✓	✓	✗	✗			
V. Regulatory proteins											
GlnE (Rv2221c)	Essential for growth of <i>Mtb</i> [121]	✓	✓	✓	✓	✓	✓	✓			
MtrA (Rv3246c)	Essential for growth of <i>Mtb</i> [122]	✗	✓	-	✓	✓	✓	✗			
DevR (Rv3133c)	Two-component system is a novel target in dormant mycobacteria [123]; essential for growth of <i>Mtb</i> under conditions of low oxygen [124]	✓	✓	✓	✗	✓	✓	✗			
DevS (Rv3132c)	Two-component system is a novel target in dormant mycobacteria [123]; part of the DevR-DevS two-component signal transduction system [124,125]	✓	✓	✓	✓	✓	✓	✓	●	●	
PknA (Rv0015c)	Possibly essential for mycobacterial growth and hence possible targets [126]	✓	✗	-	✗	✓	✓	✗			
PknB (Rv0014c)	-do-	✓	✓	✓	✗	✓	✓	✗			
PknG (Rv0410c)	Crucial virulence factor [127]; possibly essential for mycobacterial growth and hence possible targets [126]	✓	✓	✗	✗	✓	✓	✗			
PtpB (Rv0153c)	Possible target [128]	✗	✓	-	✗	✓	✓	✗			
<i>Iron Acquisition</i>											
MbtA (Rv2384)	An important adenylation enzyme required for siderophore biosynthesis [129]	✓	✓	✗	✓	✓	✓	✗			
IdeR (Rv2711)	Suggested as target [130,131]	✗	✓	-	✓	✓	✗	✗			

References

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