Target Prediction for an Open Access Set of Compounds Active against *Mycobacterium tuberculosis*

Francisco Martínez-Jiménez XII Jornadas de Bioinformática, Sevilla

One third of the world's population is infected with Mycobacterium tuberculosis, the causative agent of tuberculosis.

WHOTuber2012. Global Tuberculosis Report 2012.

Tuberculosis incidence...



MultiDrugResistant-TB



Phenotypic screening against Mycobacterium tuberculosis



Ballell, L.et al (2013). Fueling open-source drug discovery: 177 small-molecule leads against tuberculosis. ChemMedChem.

776 compounds chemical features



Phenotypic screenings



Swinney, D.C. & Anthony, J. How were new medicines discovered? Nat. Rev. Drug Discov

Finding out the mode of action...





Thursday, September 25, 14



Methods

2D-Chemogenomics Approach

Historical Approach

3D-Structural Approach

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George Papadatos

John P. Overington



Vinod Kumar

James Brown

centre nacional d'anàlisi genòm centro nacional de análisis geno



Francisco Martínez-Jiménez

Marc A. Martí-Renom









Network-based Method nAnnolyze



Applying the method, modeling genomes...











Ligand	Target	Distance	Global Z-score	Local Z-score
GSKI	pknB Kinase	1.3	-1.6	-2.5
GSKI	mapB	2.5	2.3	1.02
GSKI	sahH	1.9	-1.6	-3.16
GSKI	Mmpl3	2.6	2.42	2.97

Statistical assessment of predicted links between compounds and targets

• We merged all the predictions from the 3 methods.

•Significance of links using groups of similar compounds and the targets KEGG pathways.

•LogOdds. Odds of an observation given its probability.

 p-value using Fisher's exact test for 2x2 contingency table comparing two groups of annotations.

Compound dataset diversity



Compound dataset diversity



Targeting essential aminoacids metabolism pathways



Significant drug-protein pairs

Table 2. Significant links between GSK compound families and KEGG pathways.

GSK Family	Compound	Target	Pathways				
1	GSK975784A	Rv2182c	Glycerolipid metabolism (mtu00561)				
			Glycerophospholipid metabolism (mtu00564)				
		Rv2483c	No Pathway				
	GSK975810A	Rv2182c	Glycerolipid metabolism (mtu00561)				
			Glycerophospholipid metabolism (mtu00564)				
		Rv2483c	No Pathway				
	GSK975839A	Rv2182c	Glycerolipid metabolism (mtu00561) Glycerophospholipid metabolism (mtu00564)				
		Rv2483c	No Pathway				
		Rv2299c	No Pathway				
	GSK975840A	Rv2182c	Glycerolipid metabolism (mtu00561)				
			Glycerophospholipid metabolism (mtu00564)				
		Rv2483c	No Pathway				
	GSK975842A	Rv2182c	Glycerolipid metabolism (mtu00561)				
			Glycerophospholipid metabolism (mtu00564)				
		Rv2483c	No Pathway				
		Rv2045c	No Pathway				
		Rv2139	Pyrimidine metabolism (mtu00240)				
		Rv2299c	No Pathway				
		Rv2483c	No Pathway				
3	GSK547481A	Rv0194	ABC transporters (mtu02010)				
	GSK547490A	Rv0194	ABC transporters (mtu02010)				
	GSK547491A	Rv0194	ABC transporters (mtu02010)				
	GSK547499A	Rv0194	ABC transporters (mtu02010)				
	GSK547500A	Rv0194	ABC transporters (mtu02010)				
	GSK547511A	Rv0194	ABC transporters (mtu02010)				
	GSK547512A	Rv0194	ABC transporters (mtu02010)				
	GSK547527A	Rv1640c	Aminoacyl-tRNA biosynthesis (mtu00970)				
		Rv3598c	Aminoacyl-tRNA biosynthesis (mtu00970)				
		Rv0194	ABC transporters (mtu02010)				
	GSK547528A	Rv1640c	Aminoacyl-tRNA biosynthesis (mtu00970)				
		Rv3598c	Aminoacyl-tRNA biosynthesis (mtu00970)				
		Rv0194	ABC transporters (mtu02010)				
	GSK547543A	Rv0194	ABC transporters (mtu02010)				
7	GSK1829727A	Rv0053	Ribosome (mtu03010)				
	GRIDZYZIA	Rv0379	No Pathway				
		Rv0650	Glycolysis/Gluconeogenesis (mtu00010)				
			Galactose metabolism (mtu00052)				
			Starch and sucrose metabolism (mtu00500)				
			Amino sugar & nucl. sugar metab. (mtu00520)				

Table 2. Cont.

SK Family	Compound	Target	Pathways
	GSK1829729A	Rv3855	No Pathway
		Rv0053	Ribosome (mtu03010)
		Rv0379	No Pathway
		Rv0650	Glycolysis/Gluconeogenesis (mtu00010)
			Galactose metabolism (mtu00052)
			Starch and sucrose metabolism (mtu00500)
			Amino sugar & nucl. sugar metab. (mtu00520)
			Streptomycin biosynthesis (mtu00521)
	GSK1829816A	Rv0053	Ribosome (mtu03010)
		Rv0379	No Pathway
		Rv0650	Glycolysis/Gluconeogenesis (mtu00010)
			Galactose metabolism (mtu00052)
			Starch and sucrose metabolism (mtu00500)
			Amino sugar & nucl. sugar metab. (mtu00520)
			Streptomycin biosynthesis (mtu00521)
	GSK479031A	Rv0053	Ribosome (mtu03010)
		Rv0379	NoPathway (mtu00000)
		Rv0650	Glycolysis/Gluconeogenesis (mtu00010)
			Galactose metabolism (mtu00052)
			Starch and sucrose metabolism (mtu00500)
			Amino sugar & nucl. sugar metab. (mtu00520)
			Streptomycin biosynthesis (mtu00521)
	GSK957094A	Rv3170	Gly, Ser and Thr metabolism (mtu00260)
			Arginine and proline metabolism (mtu00330)
			Histidine metabolism (mtu00340)
			Tyrosine metabolism (mtu00350)
			Phenylalanine metabolism (mtu00360)
			Tryptophan metabolism (mtu00380)
		Rv0053	Ribosome (mtu03010)
		Rv0379	No Pathway
		Rv0650	Glycolysis/Gluconeogenesis (mtu00010)
			Galactose metabolism (mtu00052)
			Starch and sucrose metabolism (mtu00500)
			Amino sugar & nucl. sugar metab. (mtu00520)
			Streptomycin biosynthesis (mtu00521)
	GSK1188379A	Rv0194	ABC transporters (mtu02010)
	GSK1188380A	Rv0194	ABC transporters (mtu02010)
	GSK1825940A	Rv0194	ABC transporters (mtu02010)
	GSK1825944A	Rv0194	ABC transporters (mtu02010)
	BRL-10143SA	Rv1649	Aminoacyl-tRNA biosynthesis (mtu00970)
		Rv2763c	One carbon pool by folate (mtu00670)
			Folate biosynthesis (mtu00790)
			One carbon pool by folate (mtu00670)
		Rv2764c	Pyrimidine metabolism (mtu00240)
	BRL-51093AM	Rv2763c	One carbon pool by folate (mtu00670)
		Rv2764c	Folate biosynthesis (mtu00790)
			One carbon need by falate (mtu00670)

MoA Prediction against TB

Significant drug-protein pairs

GSK Family	Compound	Target	Pathways		GSK Family	Compound	Target	Pathways
1	GSK975784A	Rv2182c	Glycerolipid metabolism (mtu00561)			GSK1829729A	Rv3855 Rv0053	No Pathway Ribosome (mtu03010)
		8v2463c	Giyceropnospholipid metabolism (mtu00564)				Rv0379	No Pathway
SK Family		ing lost		Toward		Det		
ISK Family		Com	ipouna	Target		Pau	nways	
						Pyrir	midine metab	olism (mtu00240)
73		GSK1	402290A	Rv1640c		Ami	inoacyl-tRN	A biosynthesis (mtu00970)
				Rv3598c		Ami	inoacyl-tRN	A biosynthesis (mtu00970)
				Rv3834c		Ami	inoacyl-tRN	A biosynthesis (mtu00970)
				Rv3105c		No F	Pathway	
				Rv3135		No F	Pathway	
34		GSK2	270671A	Rv1284		Nitr	ogen metak	oolism (mtu00910)
5.		00112					- <u>-</u>	
				Rv3588c		Nitr	ogen metak	oolism (mtu00910)
				Rv3273		Nitr	ogen metak	oolism (mtu00910)
				Rv1707		No f	Pathway	
		Rv3598c	Aminoacyl-tRNA biosynthesis (mtu00970)					Streptomycin biosynthesis (mtu00521)
		Rv0194	ABC transporters (mtu02010)		9	GSK1188379A	Rv0194	ABC transporters (mtu02010)
	GSK547528A	Rv1640c	Aminoacyl-tRNA biosynthesis (mtu00970)			GSK1188380A	Rv0194	ABC transporters (mtu02010)
1		KV3598C	AMINOACYI-TKINA DIOSYNTHESIS (MTUUU970)		16	GSK1825940A	Rv0194	ABC transporters (mtu02010)
	GSK547542A	D-0104	ABC transporters (mtu02010)			GSK1825944A	Rv0194	ABC transporters (mtu02010)
	UJUJ4/J45A	NVU194			35	BRI -1014354	Rv1649	AminoacyLtRNA biosynthesis (mtu00970)
-	66//1000707		Kibosome (mtu03010)				Rv2763c	One carbon pool by folate (mtu00570)
7	GSK1829727A	RV0053	No Pathway					One carbon poor by forate (introdot/o)
7	GSK1829727A	Rv0053 Rv0379 Rv0650	No Pathway Glycolysis/Gluconeogenesis (mtu00010)					Folate biosynthesis (mtu00790)
7	GSK1829727A	Rv0053 Rv0379 Rv0650	No Pathway Glycolysis/Gluconeogenesis (mtu00010) Galactose metabolism (mtu00052)					Folate biosynthesis (mtu00070) One carbon pool by folate (mtu00670)
7	G5K1829727A	Rv0053 Rv0379 Rv0650	No Pathway Glycolysis/Gluconeogenesis (mtu00010) Galactose metabolism (mtu00052) Starch and sucrose metabolism (mtu00500)				Rv2764c	Folate biosynthesis (mtu00070) One carbon pool by folate (mtu00070) Pyrimidine metabolism (mtu00240)
7	GSK1829727A	Rv0053 Rv0379 Rv0650	No Pathway Glycolysis/Gluconeogenesis (mtu00010) Galactose metabolism (mtu00052) Starch and sucrose metabolism (mtu00500) Amino sugar & nucl. sugar metab. (mtu00520)			BRL-51093AM	Rv2764c Rv2763c	Folate Carbon pool by folate (mtu00070) One carbon pool by folate (mtu00670) Pyrimidine metabolism (mtu00240) One carbon pool by folate (mtu00670)

GSK1402290A attacking Aminoacyl-tRNA biosynthesis pathway

lysyl-tRNA synthetase 2

lysS1 Lysine-tRNA ligase

SERYL-tRNA synthetase SerS



nAnnolyze predicted binding-site + Autodock Vina

Experimental validation

a. MapB

b. SahH

c.AofH

d. EphA

e. SerS?

Stacey Southall EMBL

Open Access Drug Discovery

http://sgt.cnag.cat/TDI/TCAMSTB/



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CHEM GW335118X P0A546 Rx2753c total Non Essential fold drA Rx2753c MT2833 Dhydrofolate reductase (EC 1.5.1.3) mtx002790 Folate box CHEM GW335118X P0A546 Rx2753c total Non Essential fold drA Rx2753c MT2833 Dhydrofolate reductase (EC 1.5.1.3) mtx002790 Folate box CHEM GW335118X P0A546 Rx2753c total Non Essential Sol drfA Rx2753c MT2833 Dhydrofolate reductase (EC 1.5.1.3) mtx002790 Mt3002100 Metabolic put CHEM GW335118X P03572 Rx958bs total Non Essential opt Rx536s MT3694 Carbonic anhydrase (EC 4.2.1.1) (Carbonate dehydratase) mtx002790 Mt002790 Anine, ass metabolism STR GW335118X P63827 Rx1538s tosa Non Essential anxA Rx1538c MT1590 Probable L-asparaginese (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolese) mtx02420 Quenominic	on pool by folate
CHEM GW335118X P0A546 Bx/2753c tdra Non Essential IolA drfA RV2763c MT2803 Dihydrofolate reductase (EC 1.5.1.3) mb/0100 Metabolic processor CHEM GW335118X P0A546 Bx/2753c tdra Non Essential OldA drfA RV2763c MT2803 Dihydrofolate reductase (EC 1.5.1.3) mb/0100 Metabolic processor CHEM GW335118X P03572 RV1558c tdra Non Essential opnT Rv1598c MT3694 Carbonic anhydrase (EC 4.2.1.1) (Carbonate dehydratase) mb/0100 Metabolic processor STR GW335118X P03827 RV1538c tma Non Essential msA RV1538c MT1590 Probable L-asparaginase (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolase) Mato/250 Alanine, asp metabolism STR GW335118X P63827 RV1538c tma Non Essential RNn Proable L-asparaginase (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolase) mb/02400 Quanamid	osynthesis
CHEM QW335118X Q5577 Rv3588 tid Non Essential 0.36 oyn Rv3588c M1369 Carbonic anhydrase (EC 4.2.1.1) (Carbonate dehydratase) mtu00910 Nitrogen mtu00910 STR GW335118X P63827 Rv1538c tva Non Essential ansA Rv1538c M1369 MTCY48.27 Probable L-asparaginese (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolase) mtu00450 Almine, asg mtu00450 STR GW335118X P63827 Rv1538c tva Non Essential Non MTCY48.27 Probable L-asparaginese (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolase) mtu00450 Almine, asg mtu00450 mtu00460 Qynoamine	; pathways
STR GW335118X P63827 Rv1538e Image Non Essential Non Essential ansA Rv1538c MT1590 MTCV48.27 Probable L-asparaginase (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolase) mbd02250 mdb00250 Alanine, asg metabolism STR GW335118X P63827 Rv1538c Image Non Essential Non Amin An Rv1530c MT1590 Probable L-asparaginase (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolase) mbd02250 Alanine, asg metabolism STR GW335118X P63827 Rv1538c Image Non Essential Non MTCV48.27 Probable L-asparaginase (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolase) mbd0250 Alanine, asg metabolism	metabolism
STR GW035118X P63627 Rv1536 tma Rom Non ansA Rv1538c M11590 Probable L-asparaginase (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolase) mtu00460 Cyanoamino	aspartate and glutamate sm
	nino acid metabolism
STR <u>GW335118X P63627 Rv1538c Insa</u> Non Non Essential Ssential Essential MTCV48.27 Probable L-asparaginase (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolase) <u>mtu00910</u> Ntrogen me	metabolism
STR QW335118X P63627 Rv1538e Image Non Essential Non Essential ansA Rv1538e //11590 MTCV48 27 Probable L-asparaginase (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolase) mtu01100 Metabolic prime	; pathways
STR <u>GW335118X P63827 Rv1538c Insa</u> Non Non ansA Rv1538c MT1590 Probable L-asparaginase (L-ASNase) (EC 3.5.1.1) (L-asparagine amidohydrolase) mtu01110 Biosynthesis metabolites	isis of secondary les
STR QW335118X P63562 Rv1652 trd 0.05 Non Essential argC Rv1652 MT1690 MTCV06H11.17 N-acety-gamma-gutamy-phosphate reductase (AGPR) (EC 1.2.1.38) (N-acety-gutamate semialdehyde dehydrogenase) (NAGSA dehydrogenase) Macety-gamma-gutamy-phosphate reductase (AGPR) (EC 1.2.1.38) (N-acety-gutamate semialdehyde dehydrogenase) Argaine and dehydrogenase)	and proline metabolism
STR <u>GW335118X P63562</u> <u>Rv1652</u> trdf 0.05 Non argC Rv1652 MT1690 Stemial MTCV06H11.17 Metabolic participanase) (NAGSA dehydrogenase) (NAGSA dehydrogenase)	a pathways
STR 0W335118X P63562 Rv1652 trd 0.05 Non Essential arCV0652/MT1690 N-acety-gamma-gutamy-phosphate reductase (AGPR) (EC 1.2.1.38) (N-acety-gutamate semialdehyde mtu01110 Bosynthesis metabolites	isis of secondary les
STR <u>GW335118X P63562</u> Rv1652 Irdf 0.05 Non argC Rv1652 IIT1690 MTCV06H11.17 Nacetyl-gamma-gutamyl-phosphate reductase (AGPR) (EC 1.2.1.38) (N-acetyl-gutamate semialdehyde mtu01210 2-Oxocarbo	boxylic acid metabolism
STR QW335118X Q53321 Rv3171c Image Non Essential Non Essential Non Possible NON-HEME HALOPEROXIDASE HPX (EC 1.11.1) N/A No Pathway	vay



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COLLABORATORS

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