Supplementary table S1. Pairwise gene level overlap of relevant KEGG pathways in % gene content of compared pathways (pw1 and pw2, respectively).

	hsa05332	hsa0			4660		5330		04650	hsa0			05310		4672		04940		5322		4630		4514	hsa0		hsa0	
hsa05332	pw1 pw2	pw1 0 58.53	pw2 34.28	pw1 9,75	pw2 3,77	pw1 73,17	pw2 81.08		pw2 14.07	pw1 19.51	pw2 3,01	pw1 36.6	pw2 50	pw1	pw2 39.58	pw1	pw2 74.41	pw1	pw2 13,97	pw1 7,31	pw2 1,93	pw1	pw2 17.29	pw1	pw2	pw1	pw2
hsa05416	34,28 58,5		100	4,28	2,83	37,14			11,11	2,85	0,75		53,33	,	39,58			27,1	13,97	1,42	0,64	40		8,57	6,81	37,14	50
hsa04660	3,77 9,7		4,28	100	100	7,54			32,59	7,54	3,01	4,71	16,66	7,54	16,66	3,77	9,3		3,67 16.17	22,6	15,48	8,49	6,76 18,79	9,43		6,6	13,46
hsa05330 hsa04650	81,08 73,1 14,07 46,3		37,14 21,42	32,59	7,54 41,5	8,14	100 29,72		8,14 100	32,43 20,74	4,52 10,56	1,48	6,66	02,16	47,91	8,14	74,41 25,58		2,94	18,9 24,4	4,51 21,29	6,66	,	1,48	9,09 2,27	89,18 16,29	63,46 42,3
hsa04060	3,01 19,5	1 0,75	2,85	3,01	7,54	4,52	32,43	10,56	20,74	100	100	3,77	33,33	8,67	47,91		23,25	1,88	3,67	35,8	61,29	0,75	1,5	12,07	36,36	8,3	42,3
hsa05310 hsa04672	50 36,5 39,58 46,3		22,85 27,14	16,66 16.66	4,71 7,54	66,66 47,91	54,05	6,66 0	1,48 0	33,33 47,91	3,77 8,67	100 39,6	100 63,33	63,33	39,58	50 37.5	34,88 41,86		13,23 14,7	20 14,6	3,87 4,51	53,33 50	12,03 18,04	30 18,75	10,22 10,22	63,33 47.91	36,53 44.23
hsa04940	74,41 78,0		34,28	9,3	3,77	74,41	86,48	Ŭ	8,14	23,25	3,77	34,9	50		37,5		100		13,97	9,3	2,58	53,48	17,29	18,6	9,09	65,11	53,84
hsa05322	13,97 46,3		27,14	3,67	4,71	16,17	59,45	2,94	2,96	3,67	1,88	13,2	60	14,7	41,66	14	44,18	100	100	1,47	1,29	13,97	14,28	5,14	7,95	14,7	38,46
hsa04630 hsa04514	1,93 7,3 17,29 56.0		1,42 40	15,48 6,76	22,64 8,49	4,51 18.79	18,91 67,56	6,76	6,66	1,5	0,75	3,87 12	20 53,33		14,58 50		9,3 53,48	1,29	1,47 13.97	100	100	100	100	13,54	23,86 15,9	11,61 19.54	34,61 50
hsa04640	10,22 21,9	5 6,81	8,57	11,36	9,43	9,09	21,62		1,48	36,36	12,07	10,2	30	10,22	18,75		18,6	7,95	5,14	23,9	13,54	15,9		100	100	9,09	15,38
hsa05320 hsa04621	53,84 68,2 5,17 7,3	5011,72	37,14 1,42	13,46 27.58	6,6 15,09	63,46 1,72	89,18 2,7	42,3 5,17	16,29	42,3 15.51	8,3 3,39	36,5 1,72	63,33 3,33	44,23 1,72	47,91 2,08	53,8 3,44	65,11 4,65	38,5	14,7 0,73	34,6 1,72	11,61 0,64	50 0	,	15,38 5,17	9,09 3,4	100	100
hsa04810		0 4,69		13,61	27,35	0	-,,	13,61	21,48	3,28	2,64	0	0,00	0,93	4,16		2,32		2,94	4,69	6,45	5,16		4,69		o	0
hsa04150		0 0	0	25 18.81	12,26	0	0	21,15 13,86	8,14	7,69	1,5 0,37	0	0	0	0	1,92	2,32		0	21,2	7,09 1,93	0	0	0	0	0,99	0
hsa04912 hsa04062	_	0 0	0 2,85	19,04	17,92 33,96	0	0	16,4	10,37 22,96	0,99	24,52	0,52	3,33	3,7		0			0	10,6	12,9	0	0	0	0	0,99	1,92
hsa05145	12,12 39,0	2 15,9	30	23,48	29,24	15,9	56,75	11,36	11,11	12,12	6,03		60	13,63	37,5	13,6	11,00		13,97	19,7	16,77	13,63	13,53	5,3	7,95	12,87	32,69
hsa00010 hsa04120	0	0 0	0	0 2,22	0 2,83	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 6,66	0 5,8	0	0	0	0	0	0
hsa05162	5,97 19,5	1 2,23	4,28	21,64	27,35	5,97	21,62	26,86	26,66	27,61	13,96	1,49	6,66	2,98	8,33	6,71	20,93	2,23	2,2	39,6	34,19	0,74		5,97	9,09	13,43	34,61
hsa04530 hsa05214		0 12,21 0 1.53	22,85	7,63	9,43	0	0	1,00	4,44	0 9,23	0 2.26	0	0	0	0	0	0	-,	2,94 0	2,29	1,93	18,32	18,04	0	0	0	0
hsa04914		0 1,53	1,42	24,41	22,64 19,81	0		17,44	22,22 11,11	9,23	2,26	0	0	0	0	·		_	0	12,8	9,67 7,09	0	0	0	0	0	0
hsa05222	_	0 4,7	5,71	21,17	16,98	0	0	-,	5,92	0	0	0	0	0	0	0	0		0	21,2	11,61	3,52		4,7	4,54	0	0
hsa05221 hsa04910		0 1,75	1,42 0	47,36 20.28	25,47 26,41	0	0	36,84 18,11	15,55 18.51	3,5 0	0,75 0	0	0	0	0	0.72		_	0	35,1 15.2	12,9 13.54	0 0,72	0 0,75	3,5	2,27 0	0	0
hsa04122	0	0 0	0	0	0	Ō	0	0	0	0	Ō	0	Ō	0	0	0	0	0	0	0	0	0	0	Ō	0	0	0
hsa04662 hsa04370	_	0 4,1 0 5,4	4,28 5.71	68,49 47.29	47,16 33.01	0	0	,	28,88	0 2.7	0 0.75	0	0	0	0	0	0	.,	0,73	20,5	9,67 7,09	1,36	0,75 0	4,1 0	3,4	0	0
hsa05130	_	0 7,27	5,71	9,09	4,71	0	0	3,63	1,48	0	0,73	0	0	0	0	0	0	0	0	0	0	7,27	3	1,81	1,13	0	0
hsa04664	1,26 2,4	3 5,06	5,71	50,63	37,73	3,79	8,1		26,66	7,59	2,26	10,1	26,66	2,53	4,16	1,26	2,32	1,26	0,73	24,1	12,25 7.09	0	0	6,32	5,68	2,53	3,84
hsa05140 hsa05210	0 25 43,	0 11,29	10	25 33,87	16,98 19,81	21,11	54,05	15,27 30,64	8,14 14,07	8,06	4,9 1,88	23,6	00,00	1,61	2,08	27,8	46,51	31,9	0	15,3 21	8,38	25 0	13,53	18,05	14,77	22,22	30,76
hsa04114	0	0 0	0	8,18	8,49	0	0		5,92	0	0	0	0	0	0	0,9	2,32	_	0	0	0	0	0	0	0	0	0
hsa05223 hsa04310	_	0 3,7 0 2,7	2,85 5,71	44,44 10.13	22,64 14,15	0	0	48,14 10.81	19,25 11,85	3,7	0,75	0	0	0	0	0	0	_	0	27,8 4,05	9,67 3,87	0	0	0	0	0	0
hsa04380	3,12 9,7	,.	2,85	32,81	39,62	1,56	5,4		24,44	15,62	7,54	0,78	3,33	1,56	4,16	·	9,3		5,88	19,5	16,12	0	0	6,25	9,09	0	0
hsa05215 hsa05132	0 4,65 9,7	0 2,24 5 6,97	2,85 8,57	32,58 16.27	27,35 13.2	0 1,16	2.7	23,59	15,55 5,18	7,86 20.93	2,64 6,79	0	0	0 1,16	2,08		2,32 6,97		0 0,73	19,1 5,81	10,96	0	0	0 5,81	0 5,68	0	0
hsa05132	5,4 9,7		2,85		13,2	5,4		6,75	3,7	14,86	4,15	2,7	6,66	2,7	4,16			16,2	8,82	6,75	3,22	4,05		9,45	7,95	1,35	1,92
hsa04510	_	0 4,5	12,85	17	32,07	0	0		23,7	8	6,03	0	0	1	4,16	0		_	2,94	8,5		4	6,01	4	9,09	0	0
hsa00524 hsa00620	0	0 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	_	0	0	0	0	0	0	0	0	0
hsa05166	8,74 56,0	9 9,5	35,71	15,96	39,62	8,74		11,4	22,22	9,5	9,43	6,08	53,33	8,74	47,91	8,74	53,48	6,08	11,76	11,4	19,35	9,5	18,79	5,32	15,9	8,36	42,3
hsa05120 hsa04012		0 2,94 0 2,29	2,85 2.85	23,52	15,09 35.84	0	0	8,82	22.96	10,29	2,64 0,75	0	0	1,47 0	2,08	0	0	_	0	1,47	0,64	4,41 0	2,25	0	0	0	0
hsa00330	_	0 0	0	0	0	0	0	00,00	0	0	0,73	0	0	0	0	Ö	0	_	0	0	0	0	0	0	0	0	0
hsa04350	2,38 4,8		1 42	5,95	4,71	2,38	5,4 8.1		2,96	26,19 30.98	8,3	1,19	3,33	1,19	2,08 0				1,47	4,76 26.8	2,58	0	0	1,19	1,13	19.2	25
hsa04622 hsa04620	1,4 2,4 4,9 12,1		1,42 7,14	19,71 31,37	13,2 30,18	4,22 5,88		21,12 29,41	22,22	28,43	8,3 10,94	1,4 1,96	3,33 6,66	3,92		5,88			0,73 2,94	30,4	20	2,94	2,25	1,4 3,92	1,13 4,54	18,3 15,68	30,76
hsa03050	2,27 2,4		0	2,27	0,94	2,27	2,7		0,74	2,27	0,37	0	0	0	0		2,32		0,73	2,27	0,64	0	0	0	0	0	0
hsa05152 hsa05200	10,73 46,3 0,92 7,3	,=-	28,57 15,71	13,55 11,96	22,64 36,79	10,73	51,35 5,4	18,64 10,12	24,44 24,44	18,07 8,89	12,07 10,94	9,6 0	56,66	9,6 0,61	35,41 4,16	11,9	48,83 4,65	13,6	17,64	18,1 10,4	20,64 21,93	9,03 1,22	12,03	7,34 3,68	14,77 13,63	15,81 0,61	3,84
hsa04110	0	0 1,61	2,85	1,61	1,88	0	0	0	0	2,41	1,13	0	0	0,8	2,08	0	0	0	0	4,83	3,87	0	0	0	0	0	0
hsa03010 hsa05014	0 1,96 2,4	0 0 3 9,8	0 7,14	0 19,6	0 9,43	0 1,96	0 2.7	17.64	0 6,66	0 5.88	0 1.13	0 1,96	3.33	0	0	1.96	0 2,32	5,88	0 2,2	0 1,96	0 0,64	0	0	0 1,96	0 1,13	0	0
hsa04666	0	0 2,12	2,85	24,46	21,69	0	0	27,65	19,25	0	0	0	0	0	0	0	2,32	5,31	3,67	11,7	7,09	1,06	0,75	1,06	1,13	0	0
hsa04930	2,08 2,4		1 42	27,08	12,26	2,08	2,7	22,91	8,14	2,08	0,37	2,08	3,33	1.42	2.09	4,16 0			0,73	25	7,74	0	0	2,08	1,13 0	0	0
hsa05211 hsa05220	_	0 1,42 0 2,73	1,42 2,85	42,85 43,83	28,3 30,18	0	0	34,28 35,61	17,77 19,25	6,84	3,77 1,88	0	0	1,42 1,36	2,08 2,08				0	24,3 31,5	10,96 14,83	0	0	0	0	0	0
hsa04210	6,02 12,1	9 6,02	7,14	28,91	22,64	3,61	8,1	27,71	17,03	19,27	6,03	2,4	6,66	1,2	2,08	6,02			0,73	18,1	9,67	0	0	7,22	6,81	2,4	3,84
hsa05142 hsa05164	6,73 17,0 12.06 51.2		1,42 27.14	32,69 17.81	32,07 29,24	7,69 11.49	21,62 54.05	17,3	13,33 31.85	24,03 21.83	9,43	1,92 8.62	6,66 50	3,84 8.62	8,33 31,25	7,69 12.6	18,6 51,16	6,73 9.19	5,14 11.76	19,2 24,1	12,9 27.09	0 8.62	11,27	5,76 5,17	6,81	3,84 16.66	7,69 55.76
hsa05131		0 6,55	5,71	24,59	14,15	0	0	4,91	2,22	1,63	0,37	0	0	0	0	0	0	0	0	0	0	1,63	0,75	3,27	2,27	0	0
hsa04010 hsa04330	1,88 12,1	9 1,5	5,71 0	15,84	39,62	1,13	8,1	11,32	22,22	7,16	7,16	0,37	3,33	0,75	4,16 0	1,88	11,62	0,37	0,73	2,64	4,51 1 29	0	0	2,26	6,81	0,75	3,84
hsa04270	0	0 0,86	1,42	6,03	6,6	0	0	8,62	7,4	0	0	0	0	0	0	0	0	0	0	4,25	0	0	0	0	0	0	0
hsa04360		0 3,93	7,14	21,25	25,47	0			14,81	2,36		0	0		4,16				0	12.5	1.03	1,57	1,5	0	0	0	0
hsa04320 hsa00410		0 0	0	29,16	6,6 0	0				4,16 0	0,37 0	0			0	0 6,89			0	12,5 0	1,93 0	0		0	0	0	0
hsa04920	1,44 2,4	3 0	0	20,28	13,2	1,44	2,7	2,89	1,48	7,24	1,88	1,44	3,33	0	0	1,44	2,32	1,44	0,73	13	5,8	0	0	2,89	2,27	0	0
hsa05212 hsa04520		0 7,14 0 8,21	7,14 8,57		22,64	0		25,71 9.58	13,33	15,71 5,47	4,15 1,5	0			2,08 0				0 2,94	22,9 4,1		0 8,21		0	0	0	0
hsa04720		0 8,21		19,11	6,6 12,26	0			5,18 13,33	5,47	0									2,94		8,21		0	0	0	0
hsa05168	14,28 63,4	1 12,63	32,85	6,04	10,37	14,28	70,27	15,93	21,48	18,13	12,45	8,24	50	8,79	33,33	15,4	65,11	9,89	13,23	18,1	21,29			4,39	9,09	19,23	67,3
hsa05213 hsa00250		0 3,84	2,85 0	44,23	21,69	0			15,55 0	3,84	0,75 0	0	0		0	6,25			0	30,8	10,32	1,92		0	0	0	0
hsa04670	0	0 6,03	10	16,37	17,92	Ō	0	19,82	17,03	1,72	0,75	0	0	2,58	6,25	0	0	3,44	2,94	7,75	5,8	30,17	26,31	1,72	2,27	0	0
hsa05160			0 9.57		32,07	0,74			26,66	15,67	7,92					0,74			0,73	30,6	26,45		15,78	0,74	1,13	9,7	25
hsa04115 hsa04722		3 8,82 3 1,57	8,57 2,85		0,94 37,73	1,47 0,78	2,7 2,7		2,96 21,48	2,94 1,57						1,47 0,78	2,32 2,32		0	4,41 11,8	1,93 9,67	0		0	0	1,47 0,78	1,92

Supplementary table S2

Selected clinical trials showing association of MMF with diseases suggested to be associated with MMF molecular footprint by synlet enrichment between or within pathways. Only the drug association determined by synlet associated pathways is indicated, even if multiple drugs are used in a trial (as is often the case). Importantly, few trials were designed to differentiate MMF use from other drug combinations, yet apply MMF as part of basic treatment or within a list of potential treatment options.

Indication	Paired Drug	Trial	Phase	Aim	Status	Outcome
Atherosclerosis in SLE patients	-	NCT01101802	IV	MMF Efficacy	Completed	Not specified
Lupus Nephritis	-	NCT00377637	III	Superiority to Azathioprine (standard of care)	Completed	Superior
SLE with extra-renal Manifestation	-	NCT01112215	IV	Superiority to Azathioprine (standard of care)	Recruiting	-
		NCT00618527	0	Prolonging the efficacy of interferon	Ongoing	-
Multiple Sclerosis	Interferon- beta-1a	NCT00324506	II	Safety and tolerability	Unknown	-
		NCT00223301	II/III	Improvement of patient condition	Completed	Unknown
Anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis	Infliximab	NCT00753103	II	Superiority of Infliximab over standard immunosuppres sion alone	Completed	Unknown
Blood stem- cell transplantation in Chronic Myelogenous Leukemia	Interferon- alpha	NCT00110058	II	Fludarabine together with radiation + immunosuppres sion	Completed	Unknown
Lymphoblastic Leukemia and Chronic Myelogenous Leukemia	Dasatinib, Nilotinib	NCT00036738	II	Better tradeoff between graft vs. tumor and graft vs. host	Recruiting	-

Kidney Transplantation	Efalizumab	NCT00729768	II/III	Efalizumab versus Cyclosporine (in both cases MMF)	Withdrawn prior to enrollment	-
Kidney Transplantation	Efalizumab	NCT00472082	I/II	Replacement of Tacrolimus by Efalizumab	Terminated (request of the drug manufacturer)	-
Lupus Nephritis	Etanercept	NCT00447265	II	Improvement of addition to standard care (including MMF) over stabdard care alone	Terminated	-
Autoimmune diseases like arthritis	Efalizumab	NCT00777400	I/II	Superiority of Efalizumab + Sirolimus vs. Tacrolimus + MMF (Treg maximization)	Terminated (safety & trial feasibility)	-
Graft Versus Host Disease	Etanercept	NCT00639717	II	More effective prophylais	Recruiting	-
Type 1 Diabetes	Anakinra	NCT01346085	I/II	Calcineurin Inhibitor (CNI)- Free Immunosuppres sion	Ongoing	-

Supplementary table S3

This table summarizes discussed application potentials for MMF based on pathway analysis, explicit synlet network and existing clinical use. This list does not present all possibly synergistic drug combinations, only those for which certain experimental or clinical evidence exists or where extension of existing practice seems to be particularly interesting. Also, this compilation is not a complete representation of current MMF applications, particularly as it has been used in allograft transplantation and numerous auto-immune disorders to some degree.

Legend for Rationale to support a drug/disease MMF association:

- (1) Molecular footprint
- (2) SYNLET pathway enrichment (including diseases clearly implicated by a pathway)
- (3) explicit SYNLET network

Proposed Indication Rationale		Suggested relationship	Combined synlet Drugs	Most advanced level of development		
	Well esta	ablished applicat	ions and advanced trid	uls		
Allograft rejection	1/2/3	Inhibition	+ Pentostatin + Tacrolimus + Sirolimus	Standard of care		
SLE	1 / 2	Inhibition	-	Standard of care		
Multiple Colonesis	2	Tubibition	Monotherapy	Beneficial in small-scale clinical studies		
Multiple Sclerosis	2	Inhibition	+ Interferon-beta-1a	Phase II/III study; unclear status		
Vasculitis	2	Inhibition	+ Infliximab	Phase II study; unclear status		
Chagas disease	2	Amelioration or Exacerbation?	+ Pentostatin + Tacrolimus + Sirolimus	In use for heart transplantation		
Relationships	which exper	rimental/clinical	basis but which need f	urther investigation		
Inflammatory bowel			Monotherapy	Early clinical success		
diseases	2	* 1 1 1 1 1	+ Sulfasalazine	Synergy ?		
D1	3	Inhibition	Monotherapy	In use		
Rheumatoid Arthritis			+ Sulfasalazine	Synergy?		
Asthma	1/3	Inhibition	Monotherapy	Early clinical success		
Asuma	1/3	Innibition	+ Theophylline	Synergy ?		
			Monotherapy	Beneficial effect in murine model		
Atherosclerosis	3	Inhibition	Combination with drugs from the six approved groups	hypothetical		
ventricular hypertrophy / ventricular diastolic	3	Reversal?	+ Sirolimus	Clinically beneficial; Synergy?		

dysfunction						
T	1	Inhibition	Monotherapy	Lack of effect		
Type I diabetes mellitus	1		+ Anakinra	Phase I/II completed; Synergy?		
Potentially interesting	application	s/dependencies wit	hout or including on	ly sparse experimental data		
HTLV-Iinfection	2	Amelioration or Exacerbation?	+ Tofacitinib	hypothetical		
Amyotrophic lateral sclerosis (ALS)		Inhibition	-	hypothetical		
Autoimmune thyroid disease	1	Inhibition	-	?		
Viral myocarditis	1	Amelioration or Exacerbation?	-	hypothetical		
Colorectal cancer	2	Inhibition	-	In-vitro ?		
A . 1 '11 1 '	2	Inhibition	Monotherapy	In-vitro ?		
Acute myeloid leukemia		Innibition	+ Infliximab	hypothetical		
Character and a little and a	2	Inhibition	-	In-vitro ?		
Chronic myeloid leukemia	2	Innibition	+ Infliximab	hypothetical		
Pancreatic cancer	2	Inhibition	-	In-vitro?		
Renal cell carcinoma	2	Inhibition	-	In-vitro ?		
Prostate cancer	2	Inhibition	-	In-vitro ?		
Small cell lung cancer	2	Inhibition	-	hypothetical		
ErbB-1/EGFR positive cancers	2	Inhibition	+ Nilotinib + Sorafenib + Gefitinib + Panitumumab + Cetuximab	hypothetical		
Surgery (+/- Cushing's syndrome)	3	Side-effects; dosage	+ Flurane anesthetics	hypothetical		

Supplementary table S4

Potential effects of drug combinations suggested by the MMF synlet graph with or without addition of MMF. This table summarizes a number of potential interactions pointed out in the manuscript although searching for MMF independent interactions and effects of alleles was not focus of the study.

Indication	Drug combination	Proposed Effect
Antineoplastic activity	Alendronate / MMF	Antagonism
Osteoporosis, Paget's disease, Cushing's disease	Bisphosphonate drugs and Metyrapone or Mitotane with or without MMF	Synergism
Surgery / hypertension in Cushing's syndrome	Bisphosphonate drugs and Flurane anesthetics with or without MMF	Synergism ?
Studies involving MMF	SDHA inhibitors or natural variants such as SNPs	Synergism/Antagonism?; Side-effects; Clinically beneficial effect on natural SDHA variants and associated diseases such as cardiomyopathy and paraganglioma.