

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	-
Multiple Sclerosis	Interferon-beta-1a	NCT00618527	0	Prolonging the efficacy of interferon	Ongoing	-
		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 immunosuppression alone	Completed	Unknown
Blood stem-cell transplantation in Chronic Myelogenous Leukemia	Interferon-alpha	NCT00110058	II	Fludarabine together with radiation + immunosuppression	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Kidney Transplantation	Efalizumab	NCT00729768	II/III	Efalizumab versus Cyclosporine (in both cases MMF)	Withdrawn prior to enrollment	-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 standard 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 prophylaxis	Recruiting	-
Type 1 Diabetes	Anakinra	NCT01346085	I/II	Calcineurin Inhibitor (CNI)-Free Immunosuppression	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 established applications and advanced trials				
Allograft rejection	1 / 2 / 3	Inhibition	+ Pentostatin + Tacrolimus + Sirolimus	Standard of care
SLE	1 / 2	Inhibition	-	Standard of care
Multiple Sclerosis	2	Inhibition	Monotherapy	Beneficial in small-scale clinical studies
			+ 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 experimental/clinical basis but which need further investigation				
Inflammatory bowel diseases	3	Inhibition	Monotherapy	Early clinical success
			+ Sulfasalazine	Synergy ?
Rheumatoid Arthritis			Monotherapy	In use
			+ Sulfasalazine	Synergy ?
Asthma	1 / 3	Inhibition	Monotherapy	Early clinical success
			+ Theophylline	Synergy ?
Atherosclerosis	3	Inhibition	Monotherapy	Beneficial effect in murine model
			Combination with drugs from the six approved groups	hypothetical
ventricular hypertrophy / ventricular diastolic	3	Reversal ?	+ Sirolimus	Clinically beneficial; Synergy ?

dysfunction				
Type I diabetes mellitus	1	Inhibition	Monotherapy	Lack of effect
			+ Anakinra	Phase I/II completed; Synergy ?
<i>Potentially interesting applications/dependencies without or including only sparse experimental data</i>				
HTLV-I-infection	2	Amelioration or Exacerbation?	+ Tofacitinib	hypothetical
Amyotrophic lateral sclerosis (ALS)	2	Inhibition	-	hypothetical
Autoimmune thyroid disease	1	Inhibition	-	?
Viral myocarditis	1	Amelioration or Exacerbation?	-	hypothetical
Colorectal cancer	2	Inhibition	-	In-vitro ?
Acute myeloid leukemia	2	Inhibition	Monotherapy	In-vitro ?
			+ Infliximab	hypothetical
Chronic myeloid leukemia	2	Inhibition	-	In-vitro ?
			+ 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 Metirapone 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.