The establishment and validation of novel therapeutic targets to retard progression of chronic kidney disease

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The focus of this article is to define goals and resulting action plans that can be collectively embraced by interested stakeholders to facilitate new therapeutic approaches to mitigate chronic kidney disease progression. The specific goals include identifying druggable targets, increasing the capacity for preclinical and early clinical development, broadening the availability of new therapeutic approaches, and increasing investment in the development of new therapies to limit chronic kidney disease. Key deliverables include the establishment of new regional, national, and global consortia; development of clinical trial networks; and creation of programs to support the temporary mutual movement of scientists between academia and the biotechnology and pharmaceutical sector. Other deliverables include cataloging and maintaining up-to-date records to collate progress in renal research and development, inventorying the capacity of research and clinical networks, and describing methods to ensure novel drug development.

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Current status

Therapeutic strategies that positively impact the progression of chronic kidney disease (CKD) to inevitable renal replacement therapy are lacking. In proteinuric nondiabetic chronic nephropathies, blockade of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors have delayed the onset of end-stage kidney disease, as documented in the Ramipril Efficacy in Nephropathy study.[1] In parallel, ramipril-treated patients exhibited a decrease in proteinuria that was inversely correlated with the decline of glomerular filtration rate, suggesting a nephroprotective effect of reducing protein trafficking. However, dual blockade of the renin-angiotensin-aldosterone system using an angiotensin-converting enzyme inhibitor and an angiotensin II receptor blocker or a renin inhibitor have not proved to be a solution to address the existing treatment gap due to complications of hyperkalemia and acute kidney injury.[2,3] In the last 12 months, however, secondary analyses of the Empagliflozin Cardiovascular Outcome Event study in patients with diabetes mellitus at a high risk of cardiovascular disease and renal dysfunction have shown a decrease in CKD progression and a reduction in hard renal endpoints, albeit in small numbers of patients.[4] The Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results study[5] that used a glucagon-like receptor agonist in a similar population also showed renal benefit, although specific details of the renal benefit are not yet available. In the period between the positive trials of RAAS blockade and the recent trials of incretin-based therapies, there have been few phase two-four trials that

Table 1 | Recent therapeutic trials for chronic kidney disease[6]

Indication	Therapy	Status/results	Trial registration #
Diabetic nephropathy	Aldosterone receptor antagonist	Phase 2 study completed	NCT02517320
	Aliskiren (ALTITUDE)	Phase 3 study terminated due to harm[16]	NCT00549757
	Anticonnective tissue growth factor antibody FG-3019	Phase 2 study terminated due to suboptimal design	NCT00913393
	Anti-transforming growth factor-β kinase antibody (LY2382770)	Phase 2 study terminated due to lack of efficacy	NCT01113801
	Bardoxolone methyl: TSUBAKI Study, BEACON	Phase 2 study recruiting	NCT02316821
		Phase 3 study terminated due to safety concerns[17]	NCT01351675
	C-C chemokine receptor type 2 antagonism	Phase 2 study completed[18]	NCT01447147
	Dapagliflozin	Phase 4 study recruiting	NCT02682563
	Endothelin-A antagonist Atrasentan	Phase 3 study currently recruiting	NCT01858532
	Exenatide	Phase 4 study active but not recruiting	NCT02690883
	Mineralocorticoid receptor antagonist/ finerenone	Phase 2 study completed[19]	NCT01874431
		Phase 3 study recruiting	NCT02540993
	Nox1/4 inhibitor (Oral GKT137831)	Phase 2 study completed: negative results	NCT02010242
	Phosphodiesterase 5 inhibitor	Phase 2 study completed[20]	NCT01200394
	Pirfenidone	Phase 3 study recruiting	NCT02689778
	Pyridorin	Phase 3 study terminated due to lack of funding	NCT02156843
IgA nephropathy	Acthar	Phase 4 study recruiting	NCT02382523
	Blisibimod	Phase 2 and 3 study active but not recruiting	NCT02062684
	Bortezomib	Phase 4 study recruiting	NCT01103778
	Combination immunosuppression (STOP IgA)	Phase 3 study completed: negative results and a sign of harm[21]	NCT00554502
	Fostamatinib	Phase 2 study recruiting	NCT02112838
	Hydroxychloroquine Sulfate	Phase 4 study recruiting	NCT02765594
	Nefecon	Phase 2 study completed: reported positive outcomes	NCT01738035
	Rituximab	Phase 4 study recruiting	NCT02571842
	Rituximab	Phase 4 study completed	NCT00498368
	Steroids in IgA nephropathy (TESTING)	Study active but not recruiting, modified due to a sign of harm	NCT01560052
Proteinuric CKD	Curcumin	Phase 3 study completed: results not reported	NCT01831193
	LCZ696 (UK HARP-III)	Study active but not recruiting	ISRCTN11958993
Adult PKD	Metformin	Phase 2 study recruiting	NCT02903511
	Octreotide LAR (ALADIN 2)	Phase 3 study active but not recruiting	NCT01377246
	Octreotide LAR (ALADIN)	Phase 3 study competed[22]	NCT00309283
	Pioglitazone	Phase 2 study recruiting	NCT02697617
	Sirolimus	Phase 2 and3 study terminated due to safety and efficacy concerns[23]	NCT01223755
	Tolvaptan	Phase 3 study active but not recruiting in patients with CKD stage 2–4	NCT02160145
	Tolvaptan (TEMPO 3/4)	Phase 3 study completed[24,25]	NCT00428948
	Water loading	Observational study completed: results not yet reported	NCT01348035
Lupus nephritis	Abatacept	Phase 2 study completed: negative results[26]	NCT00774852
		Phase 3 study active but not recruiting	NCT01714817
	Acthar	Phase 4 study recruiting	NCT02226341
	Anifrolumab	Phase 2 study recruiting	NCT02547922
	Atacicept	Phase 2 and 3 study terminated due to safety issues	NCT00573157
	Belimumab	Phase 3 study recruiting	NCT01639339
	BI-655064	Phase 2 study recruiting	NCT02770170
	Blisibimod	Phase 3 study recruiting	NCT02514967
	Etanercept	Phase 2 study terminated: perceived risk-benefit ratio for individuals with early active RA	NCT00447265
	Infliximab	Phase 2 and 3 study terminated due to failure to recruit	NCT00368264
	Obinutuzumab	Phase 2 study recruiting	NCT02550652
	Rituximab	Phase 3 study completed: negative results[27]	NCT00282347
		Phase 3 study recruiting (as a single agent + standard of care)	NCT01673295
		Phase 2 study recruiting (in combination with Belimumab)	NCT02260934
			NCT01773616

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