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Name of Journal: *World Journal of Nephrology*

ESPS Manuscript NO: 22572

Manuscript Type: Review

To Reviewer 00102963

Comments: Excellent Basic Science Review Paper. Should Be Accepted as it Is!

Reply: The author thanks the reviewer's encouraging comments.

To Reviewer 00465176

Comments: The clinical significance of this manuscript is unclear. The authors fail to relay the message why the reader would care about the complex mechanisms involved in this pathway. The manuscript lacks focus and is too long with too many details and text. IT can be better summarized with summary figures and tables. For example rather than listing all the details in text they can present tables where they list each kinase and then in separate columns they comment on available in vitro versus in vivo data (animals vs humans) and then another column comments about future steps or if the mechanisms are unknown. Are there any therapeutic implications?

Reply: The author appreciates the reviewer's thoughtful comments that help improve the readership of this article. Therefore, the author created a sub-section in the Introduction to address the potential clinical significance of this review (page 6 to 7, marked red as all other changes). The interest in NFAT5 has significantly grown during the past few years as evidenced by the number of publications in each year. Overall, this field is just opening with a great promise for therapeutic implications. A good example is that with understanding the immunosuppressive effect of cyclosporine A resulted from its inhibition of calcineurin-mediated activation of NFAT1, clinicians are able to use cyclosporine in combination with other mechanistically different immunosupressants to improve their therapeutic efficacy and reduce their side effects. This example is also highlighted in the Abstract and Core Tip (page 2 to 3). Regarding the length of this manuscript, since the other two reviewers like the thoroughness of this article, the author chooses to leave the way it is.

To reviewer 00503339

Comments: This thorough and well written study of kinases that may intensify or block the effect of transcription factor NFAT5 is of broad interest and should prompt investigators to explore the value of blocking of microvascular disease, especially in those afflicted with diabetes. A major concern, however, is the established reality that major effects in blocking progression of vasculopathy and nephropathy in induced diabetes in rodents have not been translated to clinically useful clues to therapy in human subjects with diabetes. As examples, the high promise of blocking Advanced Glycosylated Endproduct (AGE) formation in induced diabetes in rodents based on treatment with Ruboxistaurin, Alagebrium, or Pyridoxamine all failed in clinical trials in patients. As shown in Zhou's Figure 1, the number of concurrent agents that may effect induction and progression of microvasculopathy is vast and most have still to be tested in trials of induced diabetes. Thus, this limitation in accepting the promise of initial studies in rodents should be added to the finish paper to be published. Overall, the field is just opening and should be fully studied due to its great promise.

Reply: The reviewer’s insightful suggestions have been well taken. The failed clinical trials for pyridoxamine are cited in the revised version, which serves as a premise to encourage investigators to explore alternative approaches. In this case, targeting the regulatory network of NFAT5 may hold promise to combat diabetic nephropathy more effectively (page 7, marked red as all other changes).