Diabetic Complications Consortium

Application Title: Targeted Therapeutic for Diabetic Nephropathy

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1. Project Accomplishments:

Progress on the project has been outstanding given the research restrictions due to COVID-19. We have completed the three-month animal portion for the type 1 diabetes (T1D) Akita ($Ins2^{+/C96Y}$) FVB/NJ mice. EET-F01 did not lower blood glucose levels. The laboratory has started the biochemical and histology analysis despite significant COVID-19 delays. The three-month experimental studies with the type 2 diabetes (T2D) BTBR ob/ob mice will be completed next month. Initial findings in the T2D BTBR ob/ob mice are that EET-F01 failed to lower blood glucose levels and decrease body weight.

A concern with EET analogs is there potential to enhance tumor progression. We addressed this concern in response to reviews of a study demonstrating that the kidney targeted EET-F01 decreases cisplatin nephrotoxicity. We evaluated an EET analog on the growth of a human breast cancer cell line in female athymic nude mice. The findings of these studies demonstrated that EET analogs do not stimulate tumor growth. These findings were published in the International Journal of Molecular Sciences (see publications).

COVID-19 Impact on Progress:
MCW research laboratories were under COVID-19 restrictions from the start to the end of the Diacomp project. The laboratories were under MCW Phase B2 guidelines which allowed furloughed laboratory personnel to join the laboratories. Masking and social distancing requirements meant that laboratory personnel had to work in shifts and all laboratory meetings were virtual. More importantly, due to Biomedical Resource Center staffing issues there were investigator cage limits for mice. On May 1, 2021, MCW research laboratories entered Phase C COVID-19 guidelines. Restrictions on number of research personnel in the laboratory were eased. Laboratory meetings could be in person; however, personnel are required to always wear a mask and maintain social distancing. Biomedical Resource Center staffing issues remain which limits the number of mice cages. Another issue is that the MCW Histology Core has a decreased capacity which has delayed the ability for the project to complete kidney histological analysis. In addition, there have been supply chain issues with several supplies needed to conduct the project studies. Research laboratory supplies are generally on back order for weeks to months. Laboratory supplies that include plastics have been particularly difficult to obtain. These COVID-19 restrictions slowed the pace of the project.

2. Specific Aims:

Aim: Test the hypothesis that kidney targeted EET analogs prevent the progression of TD1 and TD2 DN.

We compared two kidney targeted EET-C22 analogs to prevent the progression of T1D diabetic nephropathy. Experimental studies were conducted in T1D Akita ($Ins2^{+/C96Y}$) FVB/NJ mice. These studies demonstrated that kidney targeted EET-C22 analogs did not lower blood glucose levels. Plasma, urine, and kidneys were collected for biochemical and histological analysis. This analysis is ongoing.

Experimental studies in the T2D BTBR ob/ob mice are ongoing. T2D BTBR ob/ob mice have been treated with kidney targeted EET-C22 analogs. Initial data demonstrate that EET-F01 does not alter body weight gain or progression of diabetes in the T2D BTBR ob/ob mice. Kidney, plasma, and urine will be collected next month for biochemical and histological analysis.

3. Publications:

Imig JD, Hye Khan MA, Burkhan A, Chen G, Adebesin A, Falck JR. Kidney-targeted epoxyeicosatrienoic acid analog, EET-F01, reduces inflammation, oxidative stress, and cisplatin-induced nephrotoxicity. International Journal of Molecular Sciences 22:2793, 2021. doi: https://doi.org/10.3390/ijms22062793. PMID: 33801911

4. Other:

Kidney targeted EET technology was licensed in May 2021 to Nephraegis Therapeutics.