DiaComp Pilot & Feasibility Program - 2014

There is strong evidence that diabetic complications are linked via dysregulation of common pathways. The Diabetic Complications Consortium (DiaComp) promotes communication and collaboration between research communities investigating similar pathologic mechanisms in different organs by organizing and annual scientific meeting and funding new basic and translational research activities.

The DiaComp P&F program solicits proposals that advance the mission of DiaComp and welcomes applications that are either general in nature or that target specific areas of interest.

Applicant: CHAUDHURY, ARUN

Project Title: Defects in transcytosis may cause multiorgan diabetic complications

INDIVIDUAL CRITERIA SCORES

Please provide individual scores for the following 5 review criteria. Scores should range from 1-9 with 1 being outstanding.

1) Significance **2**

2) Investigator(s) **2**

3) Innovation **2**

4) Approach **2**

5) Environment **2**

WRITTEN COMMENTS - *please address the following points:*

·Does the proposal have high scientific merit

·Will the proposal further the mission of the DiaComp

·Will the proposal significantly advance/impact the field in the complication(s) being addressed

This proposal focuses on determining the expression and localization of myosin Va. The overall hypothesis is that in diabetes there is decreased expression of myosin Va which then affects transport of neuronal nNOS as well as glucose uptake in skeletal muscle and insulin exocytosis. The proposal focuses on determining the pattern of expression of myosin Va as well as its transcription factor snail and the localization of nNOS in enteric nerve terminals, beta cells, and skeletal muscles with the aim of potentially using skeletal muscle to infer what is going on in the gut.

In the first specific aim the expression of myosin Va and the transcription factor snail will be examined. This proposal will utilize two mouse models. The first is a model of insulin deficiency which is the Ins2Akita and the second is the db/db mouse model. The investigators state that this is a model of lean diabetes, and I am assuming that is an error given that these mice are obese and not lean and the recent epidemic is not of weight loss but rather of obesity. The experiments are carefully thought out with good preliminary data. The rationale for studying snail in this initial pilot proposal is not well outlined. The proposal would have indeed been strengthened if quantitative Western blots were also added. However, the investigator does point out the limited time period to carry out these experiments. Specific mention of controls would have been helpful. Use of more standard diabetes models in mice would also have been helpful given many the other abnormalities that may influence the results, including obesity itself.

The second specific aim will examine the membrane localization of nNOS. The preliminary data provided are in rats but they do provide a strong rationale to examine the findings in mice. Overall this specific aim is fairly straight forward and should give useful information.

Overall the proposal has several strengths including a novel approach to looking at diabetes complications with a focus on myosin Va. The investigator is well suited to carry out the proposed experiments. The proposal will provide new information and further the mission of DiaComp. Weaknesses of the proposal include a sole focus on immunohistochemistry and microscopy but the reviewer does acknowledge the short time frame for the proposed experiments. Overall the proposal should provide highly useful information for the field.

OVERALL IMPACT SCORE

Please provide an overall 'impact' score for the proposal (1-9). Feel free to weight the 5 individual scores as you see fit. It does NOT have to be the average of the 5 scores.

OVERALL IMPACT SCORE **2**