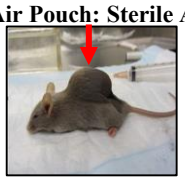
Closing the Loop for Diabetes: Extending Continuous Subcutaneous Insulin Infusion (CSII) in *Vivo*

Ulrike Klueh, PhD[1]; Chafica Kesserwan, B.S. [1]; Yi Qiao, MD[2]; Donald L. Kreutzer, PhD[2]
(1) Wayne State University, School of Engineering, Biomedical Engineering Department, Detroit, MI
(2) University of Connecticut School of Medicine, Department of Surgery, Farmington, CT

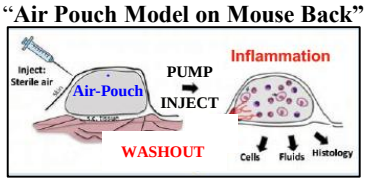
INTRODUCTION

Insulin infusion is one of the most critical components of the artificial pancreas system, yet it is the least studied. Furthermore, insulin control of blood glucose (BG) levels is critical in the clinical management of diabetes. There has been minimal effort directed towards evaluating the CSII biological interface at insulin infusion sites. This is in part due to 1) very limited number of published in vivo or clinical studies, 2) lack of characterization of the tissue reactions, 3) a lack of pertinent cellular and animal models to provide a rational foundation for enhancing insulin infusion performance. This information could lead to a better understanding of tissue toxicity at insulin infusion sites, and the extent of insulin effectiveness on BG levels in vivo.

Air Pouch: Sterile Air



"Air Pouch Model on Mouse Back"



HYPOTHESIS

1. Insulin and insulin related excipients (diluent) and products (insulin fibrils) trigger injury and inflammation at insulin infusion sites
2. Local inflammation caused by insulin and related excipients trigger adverse infusion site tissue reactions limiting the effect of insulin on blood glucose (BG) levels

EXPERIMENTAL APPROACH

Air Pouch → **Normal /Diabetic mice** **Infuse: Insulin, Diluent, Saline** **Inject: Fibrils, Thioglycolate (irritant), Saline** → Monitor BG: 3/7 Days → BG Lavage cells: FACS Histology

QUESTION 1: Does insulin, diluent, or insulin fibrils trigger inflammation in the murine Air Pouch model?

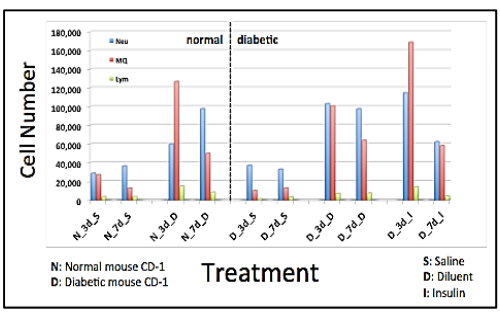


Figure 1. Air Pouch Model Diluent and Insulin Induced Inflammation: Overview of Cell Number, obtained through the use of FACS analysis following infusion of saline, diluent, or insulin for 3 and 7 days in mouse air pouch.

QUESTION 2: Does inflammation impact insulin regulation of BG in vivo?

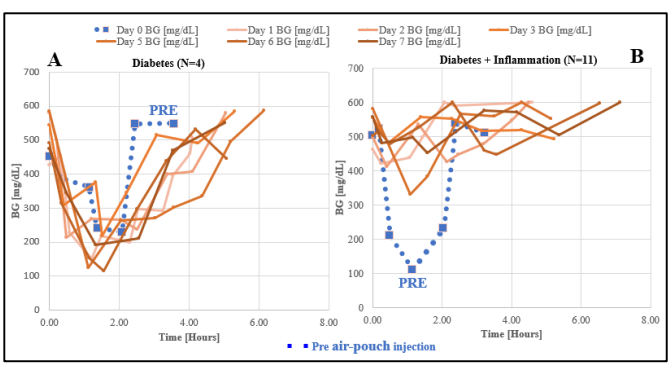


Figure 2. Impact of Thioglycolate injection on insulin function in vivo. BG Pattern of diabetic male mice injected with A) saline; B) Thioglycolate for 7-day study.
PRE= BG pattern before injecting saline or Thioglycolate

QUESTION 3: Does inflammation impact CSII and BG regulation in vivo?

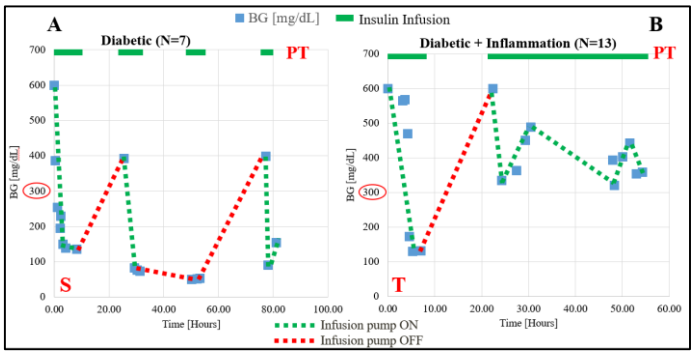


Figure 3. Impact of Thioglycolate injection on continuous insulin infusion in vivo. BG pattern of diabetic male mice injected with A) saline (S); B) Thioglycolate (T) for 3-day study. The length of insulin infusion is designated at pump

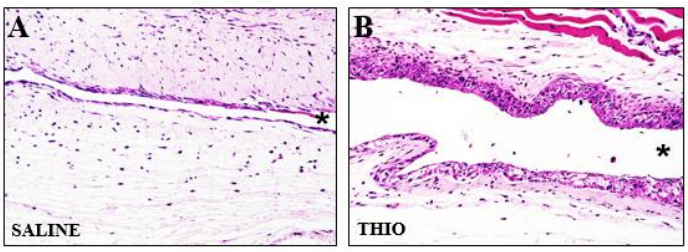


Figure 4. H&E staining of tissue reaction in diabetic murine APM injected A) Saline B) Thioglycolate followed by 3 days CSII via implanted catheter. Tissue was harvested at the end of CSII Day 3, and images taken at 20x.
* Air pouch

QUESTION 4: Can Neutrophils (PMNs) injections into air-pouch block insulin regulation of blood glucose in diabetic mice?

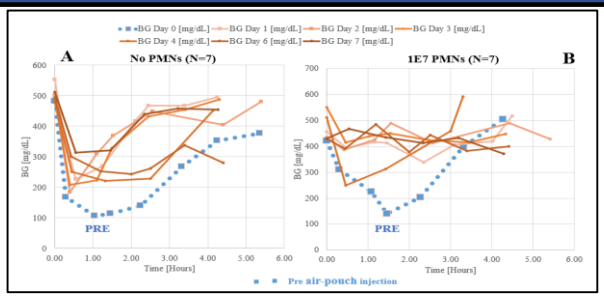


Figure 5. Impact of PMN injection on insulin function in vivo. BG pattern of diabetic male mice injected with A) saline and B) PMNs, for 7-day study.
PRE= BG pattern before injecting saline or PMNs

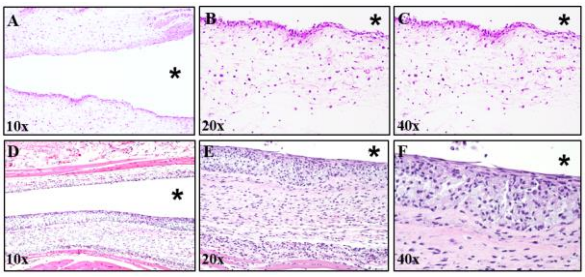


Figure 6. H&E staining of tissue reaction in diabetic murine APM injected with A, B, C) Saline and D, E, F) PMNs followed by 7 days BG monitoring. Tissue was harvested at the end of Day 7.
* Air pouch

CONCLUSION

- CSII one of the most critical elements of artificial pancreas, and also the limiting factor due to limited life-span
- Insulin and sub-components are cell and tissue toxic, and lead to tissue inflammation, and reduced effectiveness of insulin to regulate BG
- Preventing infusion/injections site inflammation will likely improve BG regulation and CSII infusion lifespan in vivo

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