Format for ANSWERING REVIEWERS

December 18, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14963-review.doc).

Title: Transplantation of Insulin-Producing Cells to Treat Diabetic Rats after 90% Pancreatectomy

Author: Yabin Yu[1], Jianmin Bian[2], Dianhua Gu[1]

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 14963

The manuscript has been improved according to the suggestions of reviewers:

1 Introduction 1) However, quality of life will be poor, this argument may not be agreed by many readers, implying suspicions on the rational of current study. 2) pancreatic cancer survival and risk of pancreatic fistula dose have little relation. 3) How about the take some cases of benign or low grade malignant tumor requiring total pancreatectomy, such as MEN, IPMT…as example supporting the rational of current study? This group of patients are highly expected for long-term survival and impaired quality of life due to total pancreatectomy

My poor expression may has caused your misunderstanding in this manuscript. I did not say quality of life will be poor, and I just said even in patients undergoing radical resection, the prognosis remains poor. Please point out it exactly. I am agree with you that pancreatic cancer survival and risk of pancreatic fistula dose have little relation. I metioned the pancreatic fistula just in order to compare pancreaticoduodenectomy and total pancreatectomy. And as you know, total panreatectomy do not cause pacreatic fistula. The incidence of Pancreatic adenocarcinoma is higher than benign or low grade malignant tumor. So I just set it as en example. In fact, our insulin-producing cells may improve long-term survival and poor life of benign or low grade malignant tumor after total pancreatectomy as well.

2 Materials and Methods IPCs were transplanted after two days of surgery. This period is thought to be in acute phase after surgery, suggesting there might be adverse inflammatory cytokine effect on implantation of IPCs. Did you check the results according to different time interval between surgery and IPC transplantation? Is there any authors' concern on this issue?

We have checked different time interval between surgery and IPCs tranplantation. And we even transplanted IPCs after one day of surgery, but these cells did not function at all. We thought the cause might be adverse inflammatory cytokine effect on implantation of IPCs as you said. Our results showed that IPCs functioned well after two days of surgery. It might associate with low immunity of UCMSCs reported by several studies.

3 Results Detection of C-peptide of differentiated cells and stimulation by high glucose -The insulin secretion is known to be regulated by neural signaling, but how single cell can detect the level of glucose in media and determine to increase the production of insulin? Insulin secretion in vivo will be constant. What is the mechanism? How can IPC have autonomy in terms with regulation of insulin secretion according to glucose level? Transplantation of IPCs Improves Glucose Tolerance in Rats after 90% pancreatectomy -Authors may need to check blood insulin and c-peptide also in order to prove effect of transplanted IPCs on serum glucose regulation. In addition, author many need to check dose-dependent outcomes according to amount of implanted IPCs How long time can transplant IPCs survive and keep functioning for glucose regulation? Were there any booster injection of IPCs to keep

glucose regulation?

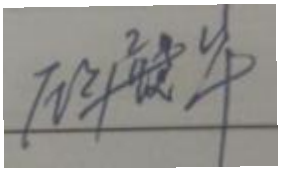
Recent studies have demonstrated the feasibility of generating insulin-producing cells obtained from human umbilical mesenchymal stem cells. These islet-like cell clusters were shown to contain human C-peptide and release insulin in response to physiological glucose levels. And our study also confirmed this. The secretion of insulin in vitro is thought to be regulated by glucose since it can easily entry into the cells and metabolize. Other mechanisms may need for further research.We have checked bood insulin and added the figure in the edited manuscript. Some studies transplanted about 5×10^6 IPCs to treat diabetic rats. We chose more cells to transplant and showed good results. The insulin levels in rats after 90% pancreatectomy transplanted with IPCs maitained at least 8 weeks in our study. How long time will IPCs die may need further research and may become a hot issue. We have not find any booster injection of IPCs to keep glucose regulation yet.

4 Discussion -Brief review on current clinical application of cell therapy for DM and future perspectives of authors in this filed will be helpful for readers.

Thank you for your advice, I have added some helpful reviews in the edited manuscript for readers.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



Dianhua Gu, MD, PhD
Department of Hepatobiliary Surgery
Huai'an First People's Hospital
NanJing Medical University
Huai'an 223300，China
E-mail: 531665908@qq.com