*Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) 2024 25(4):271-279*
www.jzus.zju.edu.cn; www.springer.com/journal/11585
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**Review**

https://doi.org/10.1631/jzus.B2300070

# Impacts of pancreatic exocrine insufficiency on gut microbiota

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**Abstract:** Pancreatic exocrine insufficiency (PEI) can be induced by various kinds of diseases, including chronic pancreatitis, acute pancreatitis, and post-pancreatectomy. The main pathogenetic mechanism of PEI involves the decline of trypsin synthesis, disorder of pancreatic fluid flow, and imbalance of secretion feedback. Animal studies have shown that PEI could induce gut bacterial overgrowth and dysbiosis, with the abundance of *Lactobacillus* and *Bifidobacterium* increasing the most, which could be partially reversed by pancreatic enzyme replacement therapy. Clinical studies have also confirmed the association between PEI and the dysbiosis of gut microbiota. Pancreatic exocrine secretions and changes in duodenal pH as well as bile salt malabsorption brought about by PEI may affect and shape the abundance and composition of gut microbiota. In turn, the gut microbiota may impact the pancreatic exocrine acinus through potential bidirectional crosstalk. Going forward, more and higher-quality studies are needed that focus on the mechanism underlying the impact of PEI on the gut microbiota.

**Key words:** Pancreatic exocrine insufficiency; Gut microbiota; Gut microbiome; Pancreatic enzyme replacement therapy

## 1 Introduction

Pancreatic exocrine acinar cells produce pancreatic juice, which is transported through the pancreatic ductal epithelium into the small intestine. It is composed of diverse digestive enzymes, such as trypsin and lipase. Pancreatic exocrine insufficiency (PEI) leads to maldigestion, with symptoms such as indigestion, digestive disorders, and weight loss. Malnutrition arising from PEI usually results in decreased levels of essential amino acids, fatty acids, microelements, fat-soluble vitamins, high-density lipoprotein C, and so on, causing osteoporosis, weakened immunity, and an increased risk of cardiovascular events (Thomas et al., 2003; Keller and Layer, 2005; Löhr et al., 2013; Working Party of the Australasian Pancreatic Club, 2016; Forsmark, 2018; Hollemans et al., 2018; Kempeneers et al., 2020). PEI is mainly triggered by chronic pancreatitis (CP), acute pancreatitis (AP), pancreatic cancer, post-pancreatectomy, post-gastrointestinal resection, diabetes mellitus, cystic fibrosis, etc. The main pathogenetic processes underlying PEI involve the reduction in trypsin synthesis caused by pancreatic exocrine function decline or exocrine acinar injury, the disorder of pancreatic juice flow due to pancreatic duct obstruction, and the imbalance of the secretion feedback mechanism, which results in a reduced stimulation of pancreatic juice production (Löhr et al., 2013; Working Party of the Australasian Pancreatic Club, 2016).

Recent studies have revealed an intimate relationship between pancreatic exocrine function and the gut microbiota. Intestinal bacterial overgrowth was found in 40.8% of CP patients and was more frequent in severe CP patients, especially those with persistent steatorrhea or weight loss, which are common clinical symptoms of PEI (Lee et al., 2019). The present review discusses and summarizes the related animal and clinical studies on the effect of PEI on the gut microbiota to reveal the potential mechanism.

## 2 Gut microbiota: composition, characteristics, and influencing factors

Trillions of organisms of more than 500 different species of bacteria commensally inhabit the gut, most

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Received Jan. 31, 2023; Revision accepted July 29, 2023;
Crosschecked Mar. 22, 2024

of which are obligate anaerobic bacteria. The microbiome in healthy individuals is characterized by an enormous diversity and functional capacity, with the most common species from Firmicutes and Bacteroidetes (Qin et al., 2010). The imbalance of interdependence and antagonism among the different microbiota, also known as dysbiosis, has been linked to altered energy homeostasis and metabolic diseases, including insulin resistance, diabetes, and obesity (Campo et al., 2019). The composition of gut bacteria is influenced by both internal and external factors. The latter include diet, environment, antibiotics, and drugs, while the internal factors are age, gender, endogenous genetics, and pancreatic exocrine function (Sekirov et al., 2010; Tilg and Adolph, 2017; Zhang et al., 2022). However, studies on the relationships between PEI and gut microbiota are still limited.

## 3 Effects of pancreatic exocrine insufficiency on gut microbiota in animal studies

Recently, several animal studies investigated the effects of PEI on the gut microbiota (Table 1). For

**Table 1 Effects of pancreatic exocrine insufficiency on gut microbiota in animal studies**

| Animal | Source of subjects with PEI | Effects on gut microbiota of PEIs | Changes in gut microbiota after PERT | Sequencing method | Reference |
|---|---|---|---|---|---|
| Dog | Ligation of pancreatic ducts | Total number of intestinal bacteria ↑; *Lactobacillus* spp. and *Streptococcus* spp. ↑ | Aerobes and anaerobes ↓ | Culture, microscopy, Gram-stained, etc. | Simpson et al., 1990 |
| Dog | Recruited through an PEI forum | Higher dysbiosis index ↑; *Escherichia coli*, *Lactobacillus*, and *Bifidobacterium* ↑; *Fusobacterium* and *Clostridium hiranonis* ↓ | *Turicibacter*, *Streptococcus*, and *Enterococcus* ↑ | Separate real-time qPCR assay | Blake et al., 2019 |
| Dog | Dogs with spontaneously occurring PEI | Bifidobacteriaceae, Enterococcaceae, and Lactobacillaceae ↑; Lachnospiraceae and Ruminococcaceae ↓; *Faecalibacterium*, *Blautia*, *Coprococcus*, *Bacteroides*, *Slackia*, and *Fusobacterium* ↓ | Not reported | 16S rRNA | Isaiah et al., 2017 |
| Mouse | | | *Akkermansia muciniphila*, *Lactobacillus reuteri*, Alcaligenaceae *Sutterella*, Clostridiaceae *Clostridium*, and Erysipelotrichaceae *Coprobacillus* ↑; Desulfovibrionales Desulfovibrionaceae, Desulfovibrionaceae *Desulfovibrio*, Desulfovibrionaceae *Bilophila*, Clostridales Lachnospiraceae, Lachnospiraceae *Dorea*, and Clostridiales Mogibacteriaceae ↓ | 16S rRNA | Nishiyama et al., 2018 |
| Pig | Ligation of pancreatic ducts | Bacteroidales, Prevotellaceae, Erysipelotrichaceae, and Enterobacteriaceae ↑; Firmicutes, Acidaminococcaceae, Ruminococcaceae, and Clostridiales ↓ | *A. muciniphila*, *Sphingomonas*, *Streptococcus*, *Mogibacterium*, *Pseudobutyrivibrio*, and *Clostridium_XI* ↑; *Corynebacterium*, *Brachybacterium*, *Kocuria*, *Tessaracoccus*, *Bifidobacterium*, *Prevotella*, *Sphingobacterium*, *Chryseobacterium*, *Empedobacter*, *Wautersiella*, *Brevundimonas*, *Ralstonia*, *Comamonas*, *Parasutterella*, *Bilophila*, *Escherihia*/*Shigella*, *Acinetobacter*, *Enhydrobacter*, *Stenotrophomonas*, *Cloacibacillus*, *Caryophanon*, *Kurthia*, *Macrococcus*, *Pseudoramibacter*, *Acetanaerobacterium*, *Dialister*, and *Selenomonas* ↓ | 16S rRNA | Ritz et al., 2020 |

PEI: pancreatic exocrine insufficiency; PERT: pancreatic enzyme replacement therapy; qPCR: quantitative polymerase chain reaction; rRNA: ribosomal RNA.

example, bacterial overgrowth was observed in the intestine of dogs with naturally developed PEI (Westermarck et al., 1993). In dogs with PEI, the total number of intestinal bacteria and dysbiosis index have been proven to be significantly increased, with the most common genera affected being *Lactobacillus* and *Bifidobacterium* (Simpson et al., 1990; Isaiah et al., 2017; Blake et al., 2019). At the same time, the abundance of *Fusobacterium* was proven to decrease in dogs with PEI compared with healthy controls (Isaiah et al., 2017; Blake et al., 2019). Moreover, the level of fecal lactate was significantly increased in dogs with PEI, which could affect the gut pH and lead to the growth inhibition of dominant bacteria (Duncan et al., 2009; Blake et al., 2019). After the administration of pancreatic secretion extracts or receiving pancreatic enzyme replacement therapy (PERT), the total numbers of aerobes and anaerobes decreased significantly. In a study by Nishiyama et al. (2018), the abundance of *Lactobacillus reuteri* and *Akkermansia muciniphila* was found to be significantly higher in the fecal samples of mice that received PERT compared to the control mice. In minipigs with PEI, the abundance of *A. muciniphila* was also found to increase significantly after PERT (Ritz et al., 2020). Both *L. reuteri* and *A. muciniphila* are considered beneficial bacteria in the gut.

According to the results of next-generation sequencing of 16S ribosomal RNA (rRNA) amplicons, both Ritz et al. (2020) and Isaiah et al. (2017) reported that the α-diversity regarding the number of observed operational taxonomic units (OTUs) and Shannon-Wiener index were decreased in subjects with PEI compared to healthy controls. After PERT, the α-diversity and Shannon-Wiener index increased significantly, with a tendency towards the α-diversity levels of healthy controls. However, for the mice without PEI, there was no significant difference in α-diversity between mice under PERT and the control mice (Nishiyama et al., 2018). Regarding β-diversity, the principal coordinates analysis (PCoA) plot showed that healthy controls clustered narrower than subjects with PEI (Isaiah et al., 2017; Ritz et al., 2020). Ritz et al. (2020) demonstrated that PERT can alter the microbial composition, with a tendency towards the abundance pattern of the healthy controls.

The above studies revealed that PEI may induce bacterial overgrowth and that the gut microbiota dysbiosis caused by PEI was diverse, which may be attenuated by PERT.

## 4 Effects of pancreatic exocrine insufficiency on gut microbiota in clinical studies

In a study conducted by Frost et al. (2019), which was based on a large group of volunteers from Pomerania with no history of pancreatic disease, the diversity of intestinal microbiomes was found to be positively associated with pancreatic elastase levels. As a promising diagnostic marker, the level of fecal pancreatic elastase has been widely applied to PEI diagnosis in recent years. Although the fecal elastase-1 test is noninvasive and convenient, its inherent bias cannot be overlooked. The sensitivity of fecal elastase-1 in the detection of mild PEI could lead to false negative results, and the watery stool samples of patients with disorders of non-pancreatic origin could lead to false positive results (Sand and Nordback, 2009; Vanga et al., 2018). Thus, precautions should be taken while interpreting the results of studies based on fecal elastase-1 tests.

Along with the variation in pancreatic exocrine function, a total of 30 taxa were found to exhibit altered abundances in the study by Frost et al. (2019). Among them, 12 taxa were negatively associated with pancreatic exocrine function, including *Prevotella*, *Catenibacterium*, *Paraprevotella*, *Slackia*, *Allisonella*, and *Solobacterium*. However, 18 taxa were positively associated with exocrine function, including *Bacteroides*, *Faecalibacterium*, *Ruminococcus*, *Flavonifractor*, *Pseudoflavonifractor*, and *Eisenbergiella*. Furthermore, Pietzner et al. (2021) performed mediation pathway analysis and found that pancreatic exocrine function impacted the availability of microbial-derived metabolites in the blood via changes in gut microbiota abundance.

Clinical studies also confirmed that bacterial overgrowth is more common in CP patients with PEI, which is in line with previous experimental results (Lembcke et al., 1985; Casellas et al., 1998). Research has revealed gut microbiota dysbiosis in CP patients with decreased diversity (Frost et al., 2020; Zhou et al., 2020). There were differences between CP patients with PEI and those without PEI in *Fusobacteria* and *Eubacterium_rectal_group* regarding the abundance of

phyla and genera in the fecal microbiomes, respectively. In CP patients with PEI, *Eubacterium_rectal_group*, *Coprococcus*, *Sutterella*, and *Eubacterium_ruminantium_group* were the dominant genera. Meanwhile, for CP patients without PEI, *Pseudomonas*, *Fusobacterium*, and *Ruminococcus_gnavus_group* were the dominant genera. Zhou et al. (2020) also found that *Bifidobacterium* was positively correlated with the level of fecal elastase-1, and that PEI may induce bacterial overgrowth and gut microbiota dysbiosis with decreased diversity.

In a study conducted by Madsen et al. (2003), fecal samples were collected from 11 CP patients with PEI, but no gut microbiota dysbiosis was detected in PEI patients compared with healthy controls. However, this may be because ten of these PEI patients had previously received PERT, and it may be inferred that the gut microbiota could be affected and normalized by PERT (Madsen et al., 2003).

## 5 Mechanisms underlying the effects of pancreatic exocrine function on gut microbiota

More recently, studies have discovered some potential mechanisms underlying the effect of pancreatic exocrine dysfunction on the composition of intestinal microorganisms as well as maintaining the balance of interdependence and antagonism among different gut microbiota. These effects of pancreatic exocrine functions could be attributed to the exocrine secretions of pancreatic acinar cells, as well as the changes in duodenal pH and bile salt malabsorption brought with PEI.

Three kinds of patterns have been described for the effects of pancreatic exocrine secretions on the gut microbiota. The first is that pancreatic exocrine-secreted peptides and proteins have regulatory or antimicrobial effects. Cathelicidin-related antimicrobial peptide (CRAMP) is excreted by pancreatic exocrine acinar cells, which are controlled by $Ca^{2+}$ channels through the endoplasmic reticulum. CRAMP showed antimicrobial activity by inhibiting the growth and permeabilizing the inner membrane of microbiota (Kościuczuk et al., 2012; Adolph et al., 2019). In the study by Ahuja et al. (2017), the excretion of CRAMP was inhibited by the genetic deletion of ORAI calcium release-activated calcium modulator 1 (Orai1), a $Ca^{2+}$ channel from pancreatic exocrine acinar cells, which resulted in moderate pancreatic injury, intestinal microbial overgrowth, and dysbiosis. In these Orai1-deficient mice, Succinivibrionaceae, *Enterobacter*, and *Prevotella* were observed to increase significantly. Finally, most of these mice died of spontaneous cluster of differentiation 3-positive ($CD3^+$) T-cell infiltration and intestinal inflammation, although they could be rescued by oral supplementation with CRAMP. Patients who carry Orai1 nonsense mutations are prone to gastrointestinal infection and diarrhea, which may be related to the above mechanism (McCarl et al., 2009). Lithostathine is another protein in pancreatic secretions. The C-terminal part of lithostathine, which is structurally related to lectins, could lead to bacterial aggregation. The aggregation of *Escherichia coli* induced by lithostathine is $Ca^{2+}$- and pH-dependent. Lithostathine might be involved in the regulation of bacterial diversity in the gut (Iovanna et al., 1993), which is in line with the gut dysbiosis observed in PEI dogs with lower concentrations of lithocholic acid compared to healthy control dogs (Blake et al., 2019).

The second pattern of pancreatic exocrine secretions involves pancreas-secreted digestive enzymes that have antimicrobial effects on the gut microbiota. For example, phospholipase A2 (PLA2) is a group of digestive enzymes, and Groups IB, V, and X are synthesized by pancreatic exocrine acinar cells. PLA2-IB has been applied to treat chronically *Streptococcus dysgalactiae*-infected lactating cows, which eliminated the organism while affecting interleukin-8 (IL-8) signaling (Buckland et al., 2000; Seroussi et al., 2018). Both PLA2-V and PLA2-X were bactericidal against Gram-positive bacteria and could kill *Listeria monocytogenes* and *Staphylococcus aureus* but not *E. coli.* Although the bactericidal activity of these PLA2s was not strong, they may play roles in modulating the diversity and composition of the gut microbiota.

The third pattern related to the effects of pancreatic exocrine secretions on the gut microbiota involves pancreas-secreted digestive enzymes, which could activate or catalyze antimicrobial activity. Trypsin, as the primary enzyme secreted by the pancreatic exocrine acinar cells, affects the gut microbiota by modulating the activity of bactericides such as pro-α-defensin. Pro-α-defensin can be catalyzed by trypsin hydrolysis into α-defensin, which can cause bacterial

agglutination and membrane perforation through electrostatic interactions (Chairatana et al., 2016). Regenerating islet-derived protein 3 (Reg3), a member of the Reg family, is a conserved C-type lectin-like protein produced by pancreatic exocrine acinar cells, which can also be catalyzed by trypsin hydrolysis (Huan et al., 2016). Activated Reg3, as a bactericide, could cause bacterial membrane perforation and inhibit mucosa-associated bacterial colonization (Shin and Seeley, 2019). PEI could cause decreased exocrine secretion of the above antimicrobial peptides and proteins as well as digestive enzymes, which could negatively affect antimicrobial component production and function.

Moreover, studies have indicated that general maldigestion induced by PEI could lead to the persistent binding of bile acids to undigested components, bringing about bile salt malabsorption (Dutta et al., 1986; Madsen et al., 2003). Apart from the gut dysbiosis observed in PEI dogs, lower concentrations of deoxycholic acid and total secondary bile acids were confirmed in these animals (Blake et al., 2019). As important signaling molecules, bile acids have been found to be activated through binding to G-protein-coupled bile acid receptor 1 or increasing the expression of farnesoid X-activated receptor, which could regulate intestinal immunity and affect antimicrobial production. Thus, it is conceivable that bile salt malabsorption in PEI could affect the diversity and composition of the gut microbiota (Nie et al., 2015; Shao et al., 2021).

The decreased pH in the duodenum due to the reduced level of pancreatic bicarbonate induced by PEI was also closely related to gut microbial composition. It has been shown that multiple *Streptococcus* strains were positively correlated with duodenal pH, while this correlation was negative for several *Prevotella* and Pasteurellaceae (Petrov, 2019; Seekatz et al., 2019).

Apart from the above changes in pH, bile salt malabsorption, the lack of pancreatic enzymes, and other factors induced by PEI, there exists a relative oversupply of food to the intestine, which may contribute to the overgrowth of dominant bacteria (Trespi and Ferrieri, 1999; Ritz et al., 2020). A previous study showed that the abundance of Firmicutes increases in male rats fed with a chow diet ad libitum (Zarrinpar et al., 2014). In addition, subjects consuming Western-style diets, also widely known as an oversupply eating pattern, host a major proportion of *Bacteroides* spp. in the gut microbiota (Dermadi et al., 2017). Firmicutes and Bacteroidetes species are both among the most common gut microbiota. Thus, the oversupply of food patterns may play a role in the development of dysbiosis, as another potential mechanism reversed by PERT.

All of the above-mentioned potential mechanisms underlying pancreatic exocrine function and PEI that affect and shape the gut microbiota are shown in Fig. 1.

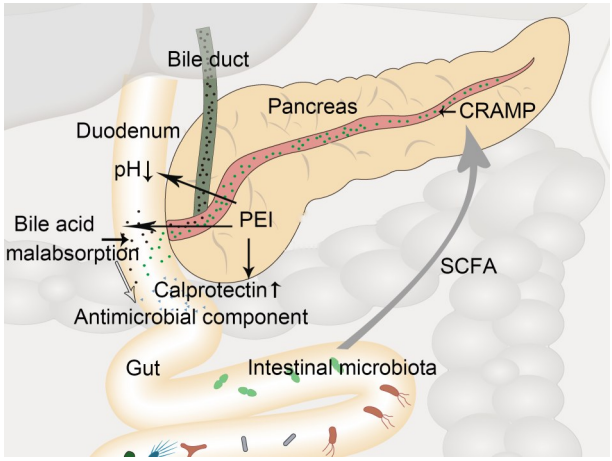


**Fig. 1 Mechanisms underlying the interplay between pancreatic exocrine function/pancreatic exocrine insufficiency (PEI) and the gut microbiota. Pancreatic exocrine function/PEI may modulate the intestinal microbiota through its secretions: antimicrobial peptides and proteins including cathelicidin-related antimicrobial peptide (CRAMP) and lithostathine; digestive enzymes that have bactericidal effects on the gut microbiota, such as phospholipase A2 (PLA2); and digestive enzymes that can activate or catalyze antimicrobials, such as trypsin that can catalyze pro-α-defensin and regenerating islet-derived protein 3 (Reg3). PEI could cause decreased exocrine secretion of the above antimicrobial peptides and proteins as well as digestive enzymes, bile salt malabsorption, and pH changes in the duodenum, which in turn could regulate intestinal immunity, affect antimicrobial component production and function, and change the diversity and composition of the gut microbiota. CRAMP could be modulated by short-chain fatty acids (SCFAs) derived from the gut microbiota, indicating a modulation-loop between the pancreatic exocrine acinus and the gut microbiota.**

## 6 Effects of gut microbiota on the pancreatic exocrine acinus

Studies have indicated that the oral administration of vancomycin could change the microbiota composition

and short-chain fatty acids, leading to increased pancreatic exocrine function with elevated amylase, elastase, and trypsin (Sileikiene et al., 2005; Reijnders et al., 2016; Girdhar et al., 2022). These studies showed that changes in the gut microbiota may affect pancreatic exocrine function, and that the potential bidirectional crosstalk between the gut microbiota and pancreatic exocrine acinus should not be underestimated. As described above, the intestinal microbiome could be affected by acinus-secreted CRAMP. CRAMP has been confirmed to be modulated by short-chain fatty acids derived from the gut microbiota. This modulation could lead to immunoregulatory environmental changes, with the phenotypic switch of intrapancreatic macrophages and changes in transforming growth factor-β (TGF-β) production, indicating a modulation loop between the pancreatic exocrine acinus and the gut microbiota (Sun et al., 2015). The above potential bidirectional crosstalk between the gut microbiota and pancreatic exocrine acinus is depicted in Fig. 1.

It has been reported that intestinal bacteria could be detected in the peripheral blood of 68.9% of AP patients, which mainly included *E. coli*, *Enterococcus*, and *Enterobacteria*. Bacteremia was related to the severity of AP (Li et al., 2013). Furthermore, in line with the study by Li et al. (2013), Tan et al. (2015) found that the levels of inflammatory factors in AP were correlated with gut dysbiosis, suggesting that gut dysbiosis may contribute to the severity of systemic inflammatory response syndrome (SIRS) during AP. AP patients complicated with infections induced by gut bacteria were prone to multiple organ dysfunctions. The above observations confirmed that gut bacterial dysbiosis was closely related to severe AP and contributed to pancreatic injury during AP, which may occur via reflux into the pancreatic duct or through the intestinal barrier (Thomas and Jobin, 2020; Lu et al., 2021). These pancreatic injuries involve both exocrine and endocrine functions, while the mechanism that elucidates the impact of gut microbiota on pancreatic exocrine acinus remains to be further explored.

## 7 Future directions

As exemplified by the above findings, gut microbiota abundance and composition may be affected and shaped by pancreatic exocrine secretions, relative oversupply of food, and changes in duodenal pH as well as bile salt malabsorption brought about by PEI. Along with the decline in dominant bacteria induced by PERT, previously diminished bacteria may increase and the relative food oversupply can be relieved. Given these beneficial effects, the gut dysbiosis induced by PEI could be partially reversed by PERT (Ritz et al., 2020).

Disturbances in the interplay between pancreatic exocrine function and the gut microbiota may cause microbial dysbiosis and related diseases. Insights into the pancreatic exocrine function–gut microbiota loop provide an important basis to guide future clinical and translational studies, which in turn contribute to the development of novel therapeutic approaches for PEI. At the same time, further studies are needed to elucidate the mechanism underlying the modulation of pancreatic exocrine function on the gut microbiota, changes in the gut microbiota induced by PEI after pancreatoduodenectomy or AP, and the crosstalk between pancreatic exocrine function and the gut microbiota.

## Acknowledgments

This work was supported by the Construction Project of Clinical Advanced Subjects of Capital Medical University (No. 1192070312), the Beijing Municipal Science & Technology Commission (Nos. Z171100001017077 and Z191100006619038), the Capital Health Research and Development of Special (No. 2020-1-2012), and the Capital Medical University Youth Science Foundation (No. PTZ21035), China.

## Author contributions

Yulin GUO designed the conception, performed the study searching and interpretation, drafted the manuscript, and revised the final manuscript. Feng CAO performed the study searching and interpretation, supervised, and revised the final manuscript. Fei LI designed the conception, supervised, and revised the final manuscript. All authors have read and approved the final manuscript, and therefore, agreed to be responsible for the research integrity and for all aspects of the work.

## Compliance with ethics guidelines

Yulin GUO, Feng CAO, and Fei LI declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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