

EUS-guided cell transplantation: Planting seeds of hope

Yunbo Jia¹, Christoph F. Dietrich², Siyu Sun¹

¹Department of Gastroenterology, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China;
²Department of Allgemeine Innere Medizin, Kliniken Hirslanden Bern, Beau Site, Salem and Permanence, Bern, Switzerland

Doctors and researchers have fought against intractable diseases such as liver decompensated cirrhosis, pancreatic cancer, and diabetes for many years, given that these illnesses are difficult to cure with drugs or surgery. Because treatment options are very limited, people affected by such devastating diseases have extremely low survival rates. Organ transplantation is the most effective radical treatment currently available. Nevertheless, the application of this technique faces several hurdles due to lack of donors and posttransplantation adverse events, including surgical trauma and immune rejection. Against this background, cell replacement therapy comes to the fore, opening a door of life for desperate patients. It is a treatment that uses the patient's own (or allogeneic) mature cells (or stem cells) to repair tissues and organs. Currently, the most representative cell therapy strategy is chimeric antigen receptor T (CAR-T) cell therapy, which uses genetic engineering techniques to generate CAR-T cells that only recognize and kill tumor cells.^[1] Cell transplantation brings cells from the laboratory to the operating room.

Stem cells, including adult stem cells, embryonic stem cells, and mesenchymal stem cells (MSCs), are the

preferred cell type for transplantation as they can differentiate into various other cell types both *in vitro* and *in vivo* under suitable culture conditions.^[2] The emergence of induced pluripotent stem cells (iPSCs) further makes autologous cell transplantation possible and helps avoid immune rejection.^[3,4] They carry exactly the same genetic material as the patient, possess similar capacity for self-renewal and pluripotent differentiation as embryonic stem cells, and overcome the ethical and technical limitations of the clinical selection of specific cells. Latest research has shown that iPSC-derived natural killer (iNK) cells can produce inflammatory cytokines and exert strong cytotoxicity against an array of hematologic and solid tumors.^[5] NK cells mediate both direct tumor lysis and T cell activation and recruitment. A robust and efficient manufacturing system for the differentiation and expansion of high-quality iNK cells was developed to fight tumors. Cell replacement therapies being investigated in ongoing clinical trials bring hope for patients with organ failure and malignancies. Over recent decades, cell therapy has progressively been introduced for several

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Jia Y, Dietrich CF, Sun S. EUS-guided cell transplantation: Planting seeds of hope. *Endosc Ultrasound* 2021;10:401-3.

Access this article online	
Quick Response Code: 	Website: www.eusjournal.com
	DOI: 10.4103/EUS-D-21-00220

Address for correspondence

Dr. Siyu Sun, Department of Gastroenterology, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China.
 E-mail: sunsy@sj-hospital.org

Dr. Christoph F. Dietrich, Department of Allgemeine Innere Medizin, Kliniken Hirslanden Bern, Beau Site, Salem and Permanence, Bern, Switzerland.

E-mail: c.f.dietrich@googlemail.com

Received: 2021-10-18; **Accepted:** 2021-12-10; **Published online:** 2021-12-27

diseases, affecting numerous parts of the body and from viscera to epidermis; these conditions include Alzheimer's disease,^[6] various cancers,^[7,8] diabetes,^[9] inflammatory bowel disease,^[10] and even the most critical disease at the moment, Coronavirus disease 2019 (COVID-19).^[11]

CAR-T cell therapy has shown great promise in some hematologic malignancies, but solid tumors have been difficult to target. One obstacle to success is that the treatment can be more toxic to normal tissues than cancer tissues. If the cells could be transplanted directly into the site of the disease, side effects would be greatly reduced. Thus, selection of the transplantation site and determination of the transplantation method are key issues in cell transplantation therapy that must be resolved urgently.

Initially, EUS was used only as a diagnostic method in the clinic. However, with the continuous development of EUS technology and endoscopic equipment, this technique can now be used in a variety of minimally invasive therapeutic interventions, such as EUS-guided fine-needle aspiration,^[12] EUS-guided celiac plexus neurolysis,^[13] EUS-guided pancreatic drainage,^[14,15] several types of EUS-guided injection and ablation procedures,^[16-19] and EUS-based human natural orifice transluminal endoscopic surgery.^[20] The continuous development of EUS technology has also opened new possibilities for cell transplantation.

Pancreatic cancer is a complex malignancy that continues to pose challenges in anticancer treatment. Cell transplantation therapy by EUS was first attempted for the treatment of pancreatic cancer early in 2000: mixed lymphocyte culture was delivered by EUS-guided fine-needle injection (FNI) to eight patients with unresectable adenocarcinoma of the pancreas.^[21] Although it could not be widely implemented, it shows feasibility of cell transplantation immunotherapy by EUS-guided FNI. Nowadays, CAR-T therapy for pancreatic cancer is included in several clinical studies. More recently, human stem cell-derived pancreatic organoids have also been generated to cure pancreatic cancer and dysfunction.^[22,23] The improvement of cell transplants increases the possibility of EUS-guided cell transplantation therapy for pancreatic cancer.

According to the statistics of the International Islet Transplantation Registry, 90% of the clinical islet transplants are completed through portal vein injection.^[24-26] However, for islet cell transplantation,

the *in situ* procedure is preferable, because the environment of the pancreas is the most suitable for islet cell survival and proliferation, and may even help stem cells differentiate into islet cells. The methods available for, however, have certain limitations: percutaneous puncture poses difficulty in accurately targeting a specific region of the pancreas, while laparoscopic techniques could be quite traumatic for patients and could easily damage the pancreas and other organs. Compared with these techniques, EUS-guided puncture requires a shorter operation time and lower cost. Further, the equipment used has good device mobility with flexible angles to reach deep abdominal structures, which allows transplantation at a precise location and is also less traumatic for patients, facilitating their faster postoperative recovery. Accordingly, EUS is especially suitable for transplantation in deep retroperitoneal organs such as the pancreas.^[27] In EUS, an ultrasonic endoscope is first inserted into the stomach, following which the transplanted cells can be precisely injected into the organs bearing the tumors, by avoiding the blood vessels of the punctured organs under the guidance of ultrasound and finding the parts with abundant blood flow for malignant cell survival and proliferation through the blood flow diagram of EUS. Furthermore, EUS can be used to perform simple imaging or cell biopsy for follow-up observation and intervention after transplantation. In some studies, islet cells were transplanted into the gastric submucosa through endoscopy so as to be conducive to biopsy evaluation for immune rejection.^[28]

EUS-guided cell transplantation is an exciting new technique falling at the crossroads of EUS and cell bioengineering. It may not only help overcome the present limitations of pancreatic cancer treatment but also expand the spectrum of therapeutic interventions for diabetes and other pancreatic ailments, resulting in improved therapeutic effect with reduced damage to surrounding tissues.

Cells, like the seeds of hope, can be precisely sowed in the soil of lesions by EUS, ensuring their exposure to optimal survival conditions without any inadvertent damage caused to the adjacent organs. EUS might thus vastly improve transplantation efficiency and further pave the way for the development of a multitude of novel therapeutic alternatives for a diverse range of diseases. EUS-based transplantation does, however, show a limitation, in that it cannot be used to transplant

large tissues or organs due to diameter limitation. Cell therapy is required to be widely applied in clinical research for the effective treatment of several diseases, and EUS gives a much-needed helping hand. However, for the translation of this new emerging technique into a safe routine procedure, researchers and endoscopists need to consider all the potential challenges that lie in the way. It is expected that future research will break through the clinical bottleneck in this field and open up an era of personalized medicine with precision cell therapy.

Conflicts of interest

Siyu Sun is the Editor-in-Chief of the journal and Christoph F. Dietrich is a Co-Editor-in-Chief. The article was subject to the journal's standard procedures, with peer review handled independently of these editors and their research groups.

REFERENCES

- DeSelm CJ, Tano ZE, Varghese AM, et al. CAR T-cell therapy for pancreatic cancer. *J Surg Oncol* 2017;116:63-74.
- Caplan H, Olson SD, Kumar A, et al. Mesenchymal stromal cell therapeutic delivery: Translational challenges to clinical application. *Front Immunol* 2019;10:1645.
- Lebreton F, Lavallard V, Bellofatto K, et al. Author correction: Insulin-producing organoids engineered from islet and amniotic epithelial cells to treat diabetes. *Nat Commun* 2020;11:5159.
- Duan B. Concise review: Harnessing iPSC-derived cells for ischemic heart disease treatment. *J Transl Int Med* 2020;8:20-5.
- Cichocki F, Bjordahl R, Gaidarova S, et al. iPSC-derived NK cells maintain high cytotoxicity and enhance *in vivo* tumor control in concert with T cells and anti-PD-1 therapy. *Sci Transl Med* 2020;12:eaa5618.
- Salwa, Kumar L. Engrafted stem cell therapy for Alzheimer's disease: A promising treatment strategy with clinical outcome. *J Control Release* 2021;338:837-57.
- Chen X, Lin X, Zhao J, et al. A tumor-selective biotherapy with prolonged impact on established metastases based on cytokine gene-engineered MSCs. *Mol Ther* 2008;16:749-56.
- Takahashi T, Omuro Y, Matsumoto G, et al. Nonmyeloablative allogeneic stem cell transplantation for patients with unresectable pancreatic cancer. *Pancreas* 2004;28:e65-9.
- Pellegrini S, Piemonti L, Sordi V. Pluripotent stem cell replacement approaches to treat type 1 diabetes. *Curr Opin Pharmacol* 2018;43:20-6.
- Sheikholeslami A, Fazaeli H, Khoshandam M, et al. Use of mesenchymal stem cells in Crohn's disease and perianal fistulas: A narrative review. *Curr Stem Cell Res Ther* 2021. [doi: 10.2174/1574888X16666210916145717].
- Shi L, Huang H, Lu X, et al. Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: A randomized, double-blind, placebo-controlled phase 2 trial. *Signal Transduct Target Ther* 2021;6:58.
- Nebel JA, Soldan M, Dumonceau JM, et al. Rapid on-site evaluation by endosonographer of endoscopic ultrasound fine-needle aspiration of solid pancreatic lesions: A randomized controlled trial. *Pancreas* 2021;50:815-21.
- Fujii-Lau LL, Bamlet WR, Eldrige JS, et al. Impact of celiac neurolysis on survival in patients with pancreatic cancer. *Gastrointest Endosc* 2015;82:46-56.e2.
- Yao Y, Zhang D, Guo J, et al. A novel self-expanding biflanged metal stent vs tubular metal stent for EUS-guided transmural drainage of pancreatic pseudocyst: A retrospective, cohort study. *Medicine (Baltimore)* 2019;98:e14179.
- Tyberg A, Bodiwala V, Kedia P, et al. EUS-guided pancreatic drainage: A steep learning curve. *Endosc Ultrasound* 2020;9:175-9.
- Yang F, Wang S, Guo J, et al. EUS-guided fine-needle technique facilitates the establishment of organoid biobanks. *Endosc Ultrasound* 2020;9:355-60.
- Kovacevic B, Kalaitzakis E, Klausen P, et al. EUS-guided through-the-needle microbiopsy of pancreatic cysts: Technical aspects (with video). *Endosc Ultrasound* 2020;9:220-4.
- Caillol F, Bosshardt C, Reimao S, et al. Drainage of the right liver under EUS guidance: A bridge technique allowing drainage of the right liver through the left liver into the stomach or jejunum. *Endosc Ultrasound* 2019;8:199-203.
- Paik WH, Park DH. Outcomes and limitations: EUS-guided hepaticogastrostomy. *Endosc Ultrasound* 2019;8:S44-9.
- Voermans RP, van Berge Henegouwen MI, Bemelman WA, et al. Feasibility of transgastric and transcolonic natural orifice transluminal endoscopic surgery peritoneoscopy combined with intraperitoneal EUS. *Gastrointest Endosc* 2009;69:e61-7.
- Chang KJ, Nguyen PT, Thompson JA, et al. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. *Cancer* 2000;88:1325-35.
- Navarro-Tableros V, Gomez Y, Brizzi MF, et al. Generation of human stem cell-derived pancreatic organoids (POs) for regenerative medicine. *Adv Exp Med Biol* 2020;1212:179-220.
- Liu X, Qin J, Chang M, et al. Enhanced differentiation of human pluripotent stem cells into pancreatic endocrine cells in 3D culture by inhibition of focal adhesion kinase. *Stem Cell Res Ther* 2020;11:488.
- Merani S, Toso C, Emamaullee J, et al. Optimal implantation site for pancreatic islet transplantation. *Br J Surg* 2008;95:1449-61.
- Arifin DR, Valdeig S, Anders RA, et al. Magnetoencapsulated human islets xenotransplanted into swine: A comparison of different transplantation sites. *Xenotransplantation* 2016;23:211-21.
- Schmidt C. Pancreatic islets find a new transplant home in the omentum. *Nat Biotechnol* 2017;35:8.
- Nigam N, Rastogi A, Bhatia V, et al. EUS-guided FNA in diagnosing pancreatic lesions: Strength and cytological spectrum. *J Cytol* 2019;36:189-95.
- Fujita M, McGrath KM, Bottino R, et al. Technique of endoscopic biopsy of islet allografts transplanted into the gastric submucosal space in pigs. *Cell Transplant* 2013;22:2335-44.