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Preface

Imaging and therapy of diabetes: State of the art

With more than 400 million patients worldwide, diabetes is one of the most prevalent diseases, and will continue to be one of the largest socioeconomic challenges in the future. While many new medications and technologies are available for the treatment of diabetes and monitoring of blood glucose levels, a cure remains elusive. Additionally, many of the available therapies are expensive and may not be efficacious for all patients. The majority of patients have type 2 diabetes, but the smaller percentage with type 1 diabetes have the increased burden of requiring continuous insulin therapy due to immune-mediated destruction of the majority of their insulin-producing cells. β-cells, located in the islets of the pancreas, are responsible for production and secretion of insulin and play a crucial role in blood glucose regulation. Defects in β-cell mass and function are the ultimate cause of both type 1 and type 2 diabetes, yet none of the therapies available directly promote improvements in β-cell mass or function. There is promise for a cure for insulin-dependent diabetes in the transplantation of functional human β-cells, but these procedures are still limited by a lack of available tissue and poor long-term graft survival and function. Therefore, there is a great need to improve our ability to target therapies to the β-cell, to measure β-cell mass and function effectively, to identify renewable sources for β-cell replacement, and to promote the long-term survival of both native and transplanted β-cells.

β-cells are located within small clusters of endocrine cells, called islets. Pancreatic islets are functional "mini-organs", containing endocrine cells (including insulin-producing β-cells and glucagon-producing α-cells) with a separate vascular system and neural system. Human pancreatic islets occupy only 1–4% of the total pancreas volume. As individual islets vary in size from 25 to 400 μm in diameter and are non-uniformly distributed throughout the pancreas, quantification is challenging through noninvasive anatomical imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT). The direct measurement of islet function *in vivo* is also challenging. Additionally, there are important differences between human and rodent islets that can limit the translation of preclinical research in islet biology. Novel approaches to image and quantify β-cell mass and function are needed to assess the efficacy of therapeutic interventions.

For those diabetes patients who require daily insulin therapy, it can be incredibly challenging to match the delivery of exogenous insulin with the metabolic needs of the body to maintain glucose homeostasis. Patients on insulin therapy invariably suffer from intermittent hyper- and hypoglycemia. New technologies to deliver insulin with more precision and less patient discomfort from frequent subcutaneous injections will help improve glycemic control and prevent complications.

Without adequate treatment, diabetes can lead to devastating microvascular and macrovascular complications. While glycemic control is an important component of diabetes care, the mortality and morbidity associated with diabetes primarily derives from these complications. Exciting advances in our understanding of the pathophysiology and novel treatment approaches for these complications will greatly improve the lives of patients with diabetes. With the tremendous advances in diabetes research over the past decade, there is a need to summarize the current status of the field and look into the future for new developments.

This *Advanced Drug Delivery Reviews* theme issue is focused on the current state-of-the-art on imaging and therapy of diabetes. The 9 review articles cover a broad range of topics in this area, which we believe will be an invaluable resource for both researchers in the field and others that are new to the topic.

In the review entitled "Therapeutic medications against diabetes: What we have and what we expect" [1], Dr. Jia and co-workers first give an overview of the commonly used antidiabetic drugs, then they review the promising therapeutic routes for treatment of diabetes such as nanotechnology, artificial pancreas, islet cell implantation, and traditional Chinese medicine. They conclude that combination of existing medications and newly developed therapies are needed for adequate control of diabetes.

In the review entitled "Molecular imaging of β-cells: diabetes and beyond" [2], Dr. Lan, Dr. Luo, Dr. Cai and co-workers gave a comprehensive review of the imaging agents that have been developed for imaging of β-cells, and the imaging techniques covered in the review include positron emission tomography (PET), single photon emission compute tomography (SPECT), magnetic resonance imaging (MRI), and optical imaging. The pros and cons of each approach are discussed along with exciting future developments expected, especially clinical translation of the most promising imaging agents for management of patients with diabetes/insulinoma, or those who receive islet transplantation.

In the review by Dr. Yang, Dr. Liu and co-workers entitled "Molecular imaging of diabetes and diabetic complications: beyond pancreatic β-cell targeting" [3], the authors provide a detailed overview of the field of molecular imaging of insulitis, imaging glucose metabolism in diabetes, as well as molecular imaging of diabetic complications such as diabetes-related coronary artery disease, diabetic cardiomyopathy, diabetic cardiac autonomic neuropathy, diabetic kidney disease, diabetic brain abnormalities, diabetes-related foot complications, among others.

In the review entitled "Advances in Transdermal Insulin Delivery" [4], Dr. Gu and co-workers summarize the exciting new bioengineering approaches in insulin therapy, such as chemical enhancer-promoted transdermal delivery, electrically facilitated transdermal delivery, mechanical force-triggered insulin delivery, and microneedle-assisted transdermal delivery which included multiple sub-categories, such as

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solid microneedles, hollow microneedles, dissolving microneedles, degradable microneedles, and bioresponsive microneedles.

In the review entitled "Strategies for improving diabetic therapy via alternative administration routes that involve stimuli-responsive insulin-delivering systems" [5], Dr. Sung, Dr. Chang, and co-workers provide an excellent overview of the different delivery strategies of insulin, which include oral delivery, intranasal delivery, pulmonary delivery, and subcutaneous delivery. The review also provides perspectives about the strategies for the future development of glucose-responsive insulin delivery systems.

In the review entitled "Advances in Immunotherapy of Type I Diabetes" [6], Dr. Chen, Dr. Zhu and co-workers first provide an introduction about pathogenesis and immunological mechanisms involved in Type 1 diabetes mellitus (T1DM). The authors describe in detail the nonautoantigen-specific T1DM immunotherapy (such as T_{reg} cell therapy, depletion of autoreactive T cells, B-cell-targeted therapy, and proinflammatory cytokine-based therapy), followed by autoantigen-specific T1DM immunotherapy (such as autoantigen-specific T or B cell modulation, and autoantigen-specific vaccines). Lastly, they also reviewed the current status of pharmacoengineering of biomaterials for T1DM treatment. They conclude that T1DM immunotherapy is entering into a new era with bright future.

In the review article entitled "Cell Encapsulation: Overcoming Barriers in Cell Transplantation in Diabetes and Beyond" [7], Dr. Grattoni and co-workers give a very detailed overview of cell-based therapy, which holds great potential for the cure of diabetes. The authors discuss cell types that have been used, the various strategies that have been investigated/developed for encapsulated cell transplantation in diabetes, as well as cell transplantation in many other diseases that may ultimately inform on diabetes. Lastly, the authors describe the key challenges to be addressed before cell-based therapies can be used in the clinic.

In the review by Dr. Ma and co-workers, entitled "Nanotechnology in cell replacement therapies for type 1 diabetes" [8], they discuss in detail the applications of nanotechnology in materials-assisted islet replacement therapy, the development of nanotechnology in macroscopic islet delivery devices, as well as the state-of-the-art of islet nanoencapsulation methods.

In the review entitled "Oxygenation Strategies for Encapsulated Islet and Beta Cell Transplants" [9], Dr. Papas and colleagues discuss in detail the critical barriers that limit the large-scale, clinical use of islet transplantation and the various potential solutions. The article specifically focuses on the challenges of oxygen delivery with encapsulation and reviews the strategies for addressing oxygen limitations to improve β-cell survival and function in implanted devices.

Together, this theme issue contains cutting-edge articles from an international ensemble of experts in the field. We are truly grateful to all of the authors for taking the time to contribute to this timely and much needed theme issue of *Advanced Drug Delivery Reviews* on the various aspects of diabetes. We sincerely hope that this issue will help to move the field forward for improved care of diabetes patients in the future.

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