The Bioartificial Pancreas, NMR and You!

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By the conclusion of this talk, attendees should be exposed to and understand the following concepts: the function of the pancreas, with emphasis on the endocrine function; Diabetes (particularly type 1); traditional therapies for type 1 diabetes; limitations of these therapies; recent alternative therapies, particularly the tissue engineered bioartificial pancreas; how NMR can aid in the monitoring of these bioartificial devices; and approaches to enhance the NMR signal (and thus information) from an implanted bioartificial construct.

Blood sugar regulation (glycemic control) is critically important in maintaining our health. In higher order animals, including us, the pancreas is the major player responsible for this regulation. Although ~98% of the pancreas functions to secrete digestive enzymes (exocrine tissue), the other 1-2%, assembled in what are known as the islets of Langerhans, secrete the endocrine hormones that regulate the blood sugar. The most numerous and arguably the most important cell in the islet is the insulin secreting β-cell.

Secretion of the hormone insulin is increased when the β-cell senses a rise in the blood glucose level, e.g., after a meal. This hormone promotes the cellular uptake, storage and utilization of glucose, facilitating energy extraction and thus lowers the glucose level in the blood. Destruction of the β-cells (generally due to an autoimmune disease) causes the insulin-dependent variety of diabetes mellitus (type-1), and results in a chronic insulin deficiency and consequent blood glucose elevation. Long-term complications from this elevation are severe, with macro- and microvascular disease a major underlying component. Complications such as nerve damage (neuropathy), kidney disease, blindness (retinopathy), stroke and vascular disease are common, even in patients obtaining treatment, though good glucose control slows disease progression.

Diabetes is a world-wide problem, predicted to affect over 330 million people by 2025 [1]. Roughly 8% of diabetics have of type-1 diabetes. The standard of care for type-1 diabetes consists of insulin delivery either through multiple daily injections or an insulin pump supplemented by injections. Although this treatment strategy affords patients a near normal life, it requires constant vigilance and cannot provide the exquisite physiologic regulation offered by native β-cells. A therapeutic approach towards curing diabetes is to replace the destroyed insulin-secreting β-cells and restore optimum blood glucose control. Methods to accomplish this include pancreatic transplantation and intra-portal islet implantations [2-4], but these approaches cannot be widely used due to scarcity of donor tissue. Moreover, recipients must receive continuous immunosuppressive medication. Alternatively, a mechanical pancreas approach combining the insulin pump with a glucose sensor has yet to fulfill its promise due to the difficulty creating a stable and accurate blood glucose sensor.   So there is

still a great need for efficacious treatments that provide physiologic blood glucose regulation without immunosuppressive medication; one that is easily administered and readily available.

A treatment that fulfills these requirements is the tissue engineered pancreatic substitute [5,6], the bioartificial pancreas. This device combines a cellular component with a non-biologic matrix and takes advantage of the cellular ability to sense glucose levels and secrete insulin accordingly. Although cells entrapped in thin sheets [7] and hollow fiber devices [8] have been actively pursued, arguably the most practical design for monitoring purposes is a macroencapsulation device (such as a disk [9]) consisting of insulin secreting cells encapsulated in materials that provide both mechanical protection [10] and partial immunoisolation [11]. The site of implantation most often used for such devices is the peritoneal cavity, and there are reports in the literature demonstrating the successful restoration of normoglycemia in diabetic animals for extended periods using encapsulated cells at this site [12,13].

Currently one determines if an implanted bioartificial pancreas is functioning properly by measuring blood glucose levels of the host. These measurements only establish if the construct is working or has failed; they cannot predict if the construct will continue to function at its current level nor for how long. NMR is a powerful technique well-suited to probe both metabolism and anatomy. An NMR-based method to non-invasively assess the viability of a bioartificial pancreatic construct was established by Stabler et al. [14,15]. This method, correlating the ^{1}H choline signal with cellular viability, was demonstrated both in vitro and in vivo on macroconstructs using a 4.7 T magnet and a surface coil as the antenna for ^{1}H detection. However, signal-to-noise issues inherent in observing a bioartificial construct with external surface coils limit the utility of this approach. To address this, we have been implementing an inductively-coupled coil system [16] at 11 T to monitor a bioartificial construct. The data show that through the use of this system, large gains in signal-to-noise can be obtained over that obtained through a surface coil, opening the way for quantitative analysis of implanted functional bioartificial organs. Development of a miniaturized multi-frequency wirelessly tunable coil system that includes important nuclei in addition to [1]H (e.g., ^{31}P, ^{19}F) is also being actively pursued.

In vivo monitoring is a significant issue in tissue engineering. The ability to monitor tissue engineered constructs in vivo can assist us to understand their function, optimize their design, and predict their failure. Performing NMR with an implantable coil enhances the sensitivity of the NMR technique and aids us in this goal. It is important to emphasize that this approach is generic and can be applied to other tissue engineered constructs.

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