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研究成果報告書

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スマートインスリンデバイスによる革新的な糖尿病治療戦略の開発

Development of novel implantable artificial pancreas, a “smart” insulin device, for treatment of diabetes

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Abstract

Diabetes is a major global health threat that poses a devastating impact on society. Among a growing lineup of medications for diabetes, insulin therapy continues to be a primary option in clinical practice for both palliative and preventive purposes. Indeed, a number of studies have shown that tight glycemic control achieved with intensive insulin regimes can effectively reduce the risk of developing or progressing the complications. Currently, the most common modality of this treatment is the patients' self-administration, termed "open-loop" insulin delivery. However, this method inevitably suffers from inaccuracy of the dose control, where the overdose must be strictly avoided otherwise causing acute and fatal hypoglycemia. Recently, a growing effort has been focused on the development of a "closed-loop" or a self-regulated type of insulin delivery system that is able to continuously deliver more accurate amount of insulin in response to the change in blood glucose concentrations. These systems, so-called "artificial pancreas", typically combine subcutaneously implanted glucose sensors and automated algorithm-driven insulin infusing modules that are either electrically or wirelessly communicable. Whilst accumulating reports validate this approach, limitations also persist. As for "electronics-derived" issues, the need for frequent calibration and maintenance may impair ease of use and thus the users' QOL. In addition, these technologies may raise the therapeutic cost for diabetes.

In stark contrast to the above, our study focuses on a "protein-free", totally synthetic approach, taking advantage of boronate-sugar binding chemistry. Boronic acid (BA) derivatives readily complex with 1,2- and 1,3-cis-diols, including those present in glucose, through reversible boronate ester formation. In this study, we showed that the boronate gel–based insulin-diffusion control mechanism is weekly sustainable while also being acutely glucose-responsive on a timescale of tens of seconds, features potentially meeting the current unmet needs in insulin therapy, including the management of glucose spikes. Thus, we created a catheter-combined device scaled suitable for mouse experiments, which, upon subcutaneous implantation, could control the glucose metabolism under both insulin-deficient and insulin-resistant conditions with at least 3-week durability. Then, we produced a hemodialysis (semipermeable) fiber-combined device by installing a thin coat of the gel throughout the fiber surface but not within, thereby achieving both a dramatically increased diffusion-active surface area (as compared to the previously reported catheter-combined type) and a smooth supply of insulin. And finally, we developed a microneedle-combined device in order to dramatically reduce stress and invasion to patients. Our "smart-gel" technology could offer user-friendly and remarkably economic (disposable) alternative to the current state-of-the-art, thereby facilitating availability not only to

diabetic patients in developing countries, but also to those who otherwise may not be strongly motivated such as the elderly, infants and patients in need of nursing care.