Journal of Diabetes Science and Technology
Volume 1, Issue 3, May 2007

New Technologies for Diabetes Presented at International Congresses in 2006

Viera Donicova, M.D., Ph.D.

Abstract

Diabetes is a medical specialty that is currently experiencing the rapid development of new technologies that can be applied to clinical management. At three international Diabetes Congresses held in 2006 (the annual meeting of European Association of Diabetes in Copenhagen, the World Congress of the International Diabetes Federation in Cape Town, and the Diabetes and Technology meeting in Atlanta), several new technologies and devices were demonstrated that are applicable to diabetes care. Out of various technological innovations, this article highlights three new interesting areas, which may represent the principal direction of future developments in science that may help improve the quality of life for the person with diabetes.

J Diabetes Sci Technol 2007;1(3):445-450

Metabolism and Weight Management

One significant development related to metabolism involves the field of nutrition and weight control. The rising prevalence of the twin problems of obesity and diabetes has reached epidemic dimensions on a global scale as a consequence of major changes in lifestyle, with reduced physical activity being combined with the excessive consumption of high-energy foods in adults, children, and adolescents. Because a basic requirement for modifying the lifestyle of an individual patient is an objective documentation of prevailing dietary habits and behavior relevant to energy balance, defining a baseline for the physician and also for the patient is important.

A continuous monitor of energy expenditure and of spontaneous physical activity, the SenseWear armband (BodyMedia, Inc., Pittsburgh, PA) is a relatively new device that can be worn on the upper arm, which can provide objective information to reveal the nature of the patient's lifestyle and of their response to prescribed therapy, including the effect of medications or physical rehabilitation measures. Compared to other "metabolic monitors," this system includes two important new features. First, because all measurements are performed in "free-living" conditions, this system can be used at work, at school, during sporting activities, and during the night.

Author Affiliation: Clinical Advisory Board, Journal of Diabetes Science and Technology

Abbreviations: (DSPB) Department of Special Polymers and Biopolymers, (HOMA-IR) homeostasis model assessment method, (METs) metabolic equivalents, (nCPAP) nasal continuous positive airway pressure treatment, (OSA) obstructive sleep apnea, (SBD) sleep-related breathing disturbances

Keywords: continuous glucose monitoring, diabetes, encapsulated cell technologies, energy expenditure measurement, Langerhans islet transplantation, metabolic Holter, obesity, obstructive sleep apnea

Corresponding Author: Viera Doničová, M.D., Ph.D., Furčianska 69, 04014 Košice, Slovakia, Europe; email address viera.donicova@gmail.com

Second, monitoring can continue for up to 2 weeks and gives a representative picture of daily energy expenditure. This armband device has incorporated a "SenseWear" display, a type of Holter monitor in a wristwatch form, which displays calorific consumption and duration of physical activity.

The armband is now available commercially for clinical and research use, as a scientifically validated "metabolic, physical activity and lifestyle Holter."[1–3] It weighs 82 g and measures 8.8 × 5.6 × 2 × 1 cm. This Holter-style monitor simultaneously measures several physiological parameters (skin temperature, galvanic skin response, heat flux, and body motion). It provides an estimation of energy expenditure based on specific algorithms. The armband documents the duration of any physical activity performed by the individual above a predetermined level of intensity measured in metabolic equivalents (METs) (kcal/kg/h), in addition to the number of steps taken (**Figure 1**). METs are used in medicine to quantify the energy consumption of different activities, so the armband can measure metabolic "physical activity."

The main parameters evaluated by the software in SenseWear are as follow.

1. The basal metabolic rate (average energy expenditure during resting hours).

2. The energy expenditure through spontaneous, moderate, or high intensity physical activity.

3. The status of physical fitness by recording the peak of METs achieved during high intensity physical activity, in addition to the daily METs that characterize the nature of the patient's lifestyle (e.g., sedentary).

4. The duration and quality of sleep.

The duration and quality of sleep are important parameters recorded by the SenseWear armband. It is known that being overweight can disrupt normal sleep architecture, and obesity is associated with sleep disorders of differing severity.[4] From data obtained over several days with the armband, the relative ratio between lying flat and sleep can be examined, and potential sleep disorders can be suspected, which can be then be investigated further using polysomnography.

Accurate recording of energy expenditure is useful in developing a rational individual approach to long-term weight loss. Knowledge of caloric consumption allows small reductions to be made in the daily caloric intake. Over a period of time, such caloric deficits are easier for patients to accept and, when combined with increased physical activity, should result in a progressive and selective loss of body fat with minimal changes in lean body mass and basal metabolic rate. The professional software version, which is optional, also shows details of the test and provides both raw and calculated data (in Excel) for further evaluation. Data from the armband can be discussed with patients and offer a personalized approach to management. Data demonstrate the individual's lifestyle pattern throughout each day and can be compared with a diary report of physical activity. Discrepancies can be discussed with patients and may act as a motivational and educational tool. Repeated measurements with the SenseWear armband can demonstrate objectively the improvements achieved by physical activity and dietary management, showing an elevation of basal metabolic rate in relation to an increase in bioactive cell mass (mainly muscle mass) during weight reduction (mostly associated with a reduction in body fat).

Many physicians are now purchasing the SenseWear armband device for determination of energy expenditure in conditions such as diabetes, obesity, metabolic disorders, endocrinology, and gastroenterology, and its application is of interest to cardiologists, neurologists, psychiatrists, and specialists in internal medicine, sports medicine, and occupational health. It provides a method to observe "objectively" the behavior of patients and their responses to treatment during normal daily life through several indices and parameters associated with spontaneous and/or programmed physical activity. This device looks very promising in assisting with the rational approach to the treatment of obesity and type 2 diabetes, as it allows tailoring the dietetic treatment based on the actual energy expenditure of the patient. It is certainly an innovative device in metabolic medicine that can provide a valuable adjunct to medical treatment.

The SenseWear armband was exhibited successfully in Boston at the North American Association for the Study of Obesity in 2006 as a "metabolic, physical activity and lifestyle Holter." In September 2006 it was included in the Italian project, Telbios (www.telbios.it).

Diabetes, Sleep, and Breathing Disturbances

There is rising evidence from epidemiological and scientific work about the relationship and mutual influence of glucose metabolism and respiration.

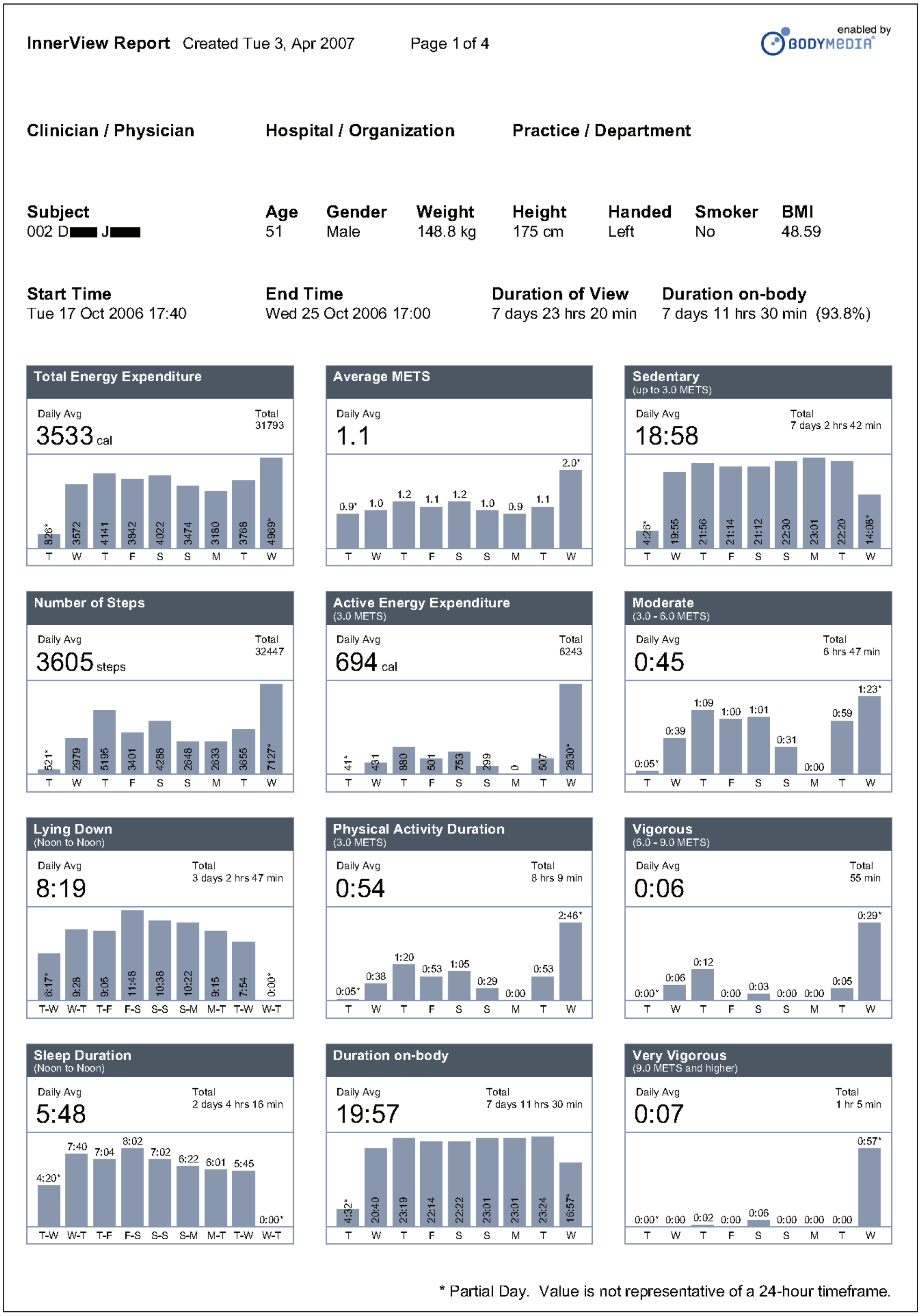

Figure 1. SenseWear armband activity: a lifestyle report from an 8-full-day measurement of a 51-year-old man with a body weight of 148.8 kg. His daily total energy expenditure was 3204 kcal, and an average duration of physical acitivity during 1 day of measurement was 49 min with an average active energy expenditure of 625 kcal. The duration of physical activity (above the set threshold of 3.0 METs) amounted to only 38 min on Wednesday, 1 h 20 min on Thursday, but 2 h 51 min on the second Wednesday (refer to middle graph on top row). These durations correspond to active energy expenditures of 299 to 800 kcal except for the last Wednesday with 2878 kcal (refer to second graph in first column). On this day the person reached 1.7 METs, did almost 8241 steps, and had a physical activity duration of 2 h 51 min. Patient had poor sleep efficiency (with only 5 h 52 min of sleep a day in contrast with staying in bed for 7 h 35 min). His average metabolic equivalent was 1.1 kcal/kg/h, which represents a typical activity-related lifestyle of an obese or inactive person.

Sleep experts have noted marked modulator effects on glucose metabolism and molecular mechanisms. In laboratory studies of healthy young adults submitted to recurrent partial sleep restriction, marked alterations in glucose metabolism, including decreased glucose tolerance and insulin sensitivity, have been demonstrated.[5] Epidemiological evidence supports an association between short sleep duration and the risk for obesity and diabetes.

More profound clinical and scientific evidence about the relationship between diabetes and sleep-related breathing disturbances (SBD) was found in obstructive sleep apnea (OSA). OSA is a syndrome characterized by the cessation of breathing during sleep with apneic episodes, caused by upper airway collapse, which can occur repetitively hundreds of times a night. It is connected with sleep fragmentation and hypoxia, which likely can provoke and exaggerate the severity of metabolic disturbances. The resulting pathophysiological changes may lead to vascular disease. Obstructive sleep apnea appears as an independent comorbid factor in cardiovascular and cerebrovascular diseases. OSA is also independently associated with insulin resistance and type 2 diabetes. There is a three times higher risk of development of diabetes in patients with OSA not caused only with obesity.[6] From the opposite point of view, diabetic patients demonstrate comorbidity, similar to patients with OSA. The Sleep Heart Health Study[7] has shown that diabetes is associated with periodic breathing and respiratory abnormalities in the central control of ventilation. The high prevalence of SDB in diabetes suggests the presence of a potentially treatable risk factor for cardiac vascular diseases in the diabetic population.

Insulin resistance is a known risk factor for atherosclerosis, and OSA represents a stress that promotes insulin resistance, hence atherogenesis. A study by Ip and colleagues[8] investigated the relationship between SBD and insulin resistance, indicated by the fasting serum insulin level and the insulin resistance index based on the homeostasis model assessment method (HOMA-IR). Each additional apnea or hypopnea per sleep hour increased the fasting insulin level and HOMA-IR by about 0.5%. Pallayova and co-workers[9] showed the association of glucose elevation with apneic episodes in sleep apnea patients on continuous glucose tracing with their ameliorating (**Figure 2**) under nasal continuous positive airway pressure treatment (nCPAP). The specific treatment modality of OSA with nCPAP (a device that, through a nasal mask during sleep, applies an air column under pressure that keeps the upper airway open) improved insulin sensitivity[10] and, after longer than 4 hours of application per night, significantly reduced postprandial glucose values and glycated hemoglobin.[11] The drop of glycated hemoglobin (Hb1C) correlated with the duration of nCPAP treatment.

The field of diabetes in connection to sleep and breathing is one of the hot topics under development discussed at medical conferences. The ResMed, world leader in nCPAP device manufacturing, has created a new division of research (diabetes and sleep apnea). It is hoped that with improvement of ventilation and oxygenation by treatment in affected subjects we can improve these glucose metabolism parameters. The metabolic interconnection of human body systems should be taken into account in our medical and scientific thinking and should guide our actions in research and treatment.

Encapsulated Cell Technologies

One of the most promising approaches in transplant research is focused on encapsulation. These technologies may protect the transplanted cells from immune rejection by an artificial, semipermeable membrane, potentially allowing transplantation without the need for immunosuppression. The concept of microencapsulation in polymeric semipermeable membranes was established by Chang in 1964.[12] However, despite some encouraging results in animal studies, this technique has not lived up to expectations, and clinical products based on encapsulated cell technology continue to elude the scientific community. Important considerations with respect to obtaining consistent clinical success with cell encapsulation include a source of functional cells and a mechanically and chemically stable membrane of suitable permeability and biocompatibility, in addition to biosafety and long-term survival of the graft. Some interesting research developments have taken place in recent years that have focused on the identification of alternative natural and synthetic materials for use in cell encapsulation.

Eastern and central European countries have a long tradition and effective track record in this field, including the work of Professor Korec in Slovakia with his successful transplantation model of islets of Langerhans in 1991.[13] Also in Slovakia, a new Department of Special Polymers and Biopolymers (DSPB) was created in 2002 in the Science Polymer Institute of Slovak Academy. DSPB studies polymer chemistry in the development and application of materials for encapsulation technologies and for materials used for implanted biosensors. This laboratory has established a reputation in the field of pancreatic islet transplantation for the treatment of diabetes

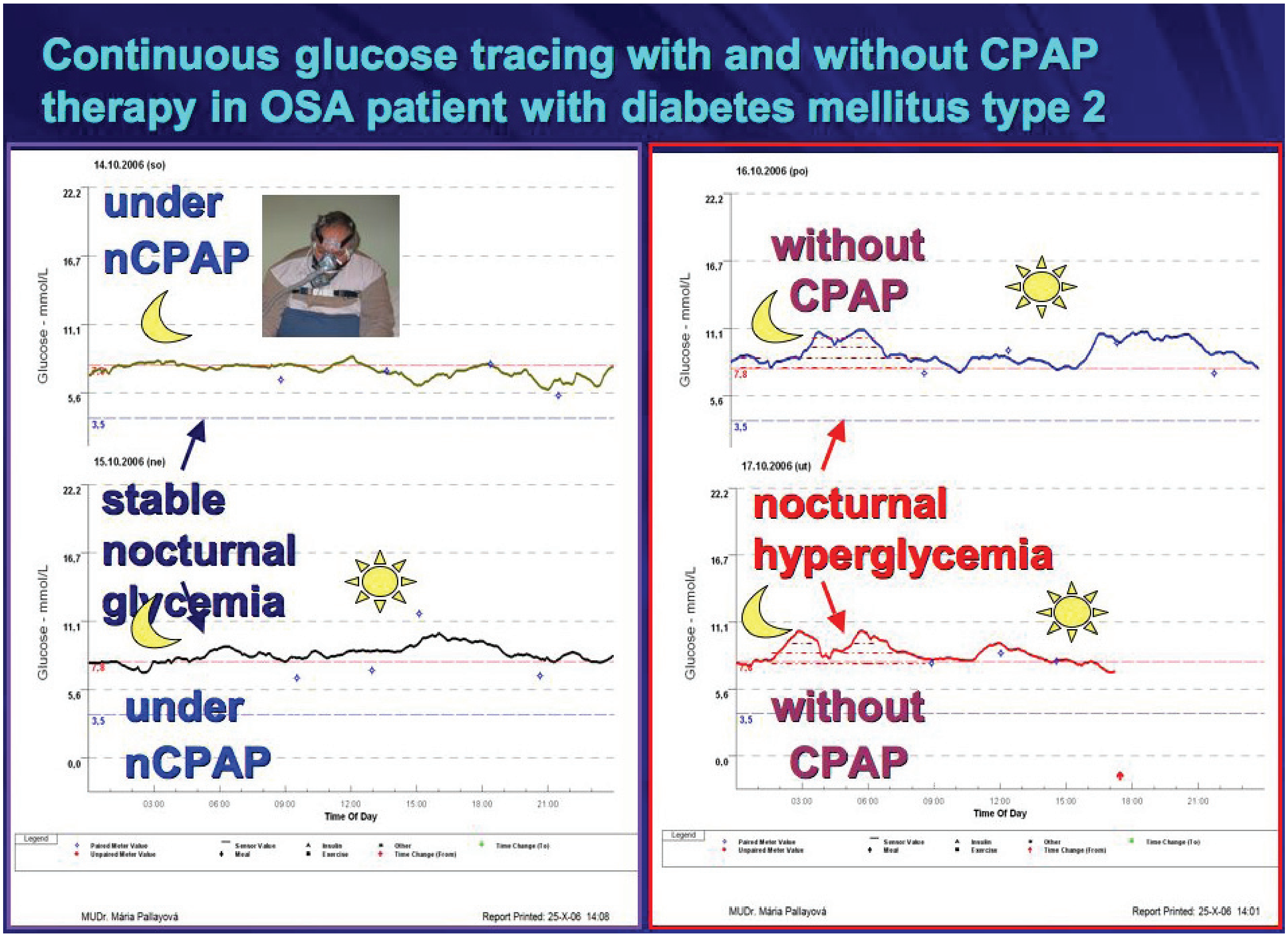

Figure 2. Glycemic consequences of skipping nCPAP therapy in a type 2 diabetic patient with severe sleep apnea are shown. During the first 2 nights under nCPAP (therapy), continuous glucose monitoring showed stable nocturnal glycemia. However, unusual nocturnal hyperglycemic episodes were observed during the following 2 nights without nCPAP. This therapy resulted in a significant decrease of mean nocturnal glycemia and improved area under the 2-h blood glucose response curve of >7.8 (0–480 min). Continuous glucose monitoring also showed improved preprandial and 1.5-h postprandial glycemias for breakfast after nCPAP nights.[9]

(www.polymer.sav.sk/lacik.html). In 2005, this group successfully completed a project examining the immobilization of biological systems that target the regulation and transfer of nano-sized bioactive substances through highly defined polymeric membranes. The main contributions of this research group have been to develop novel mechanisms of microcapsule formation and to successfully bridge the properties of these microcapsules with transplantation *in vivo*.

One of the main challenges posed by cell encapsulation is the biocompatibility of the material, which must not provoke a strong immunogenic reaction that would result in formation of a thick layer of fibrous tissue covering the surface of the membrane (so-called biofouling). When this occurs, the diffusion of nutrients and oxygen is reduced drastically, causing islet necrosis and transplant failure. However, the formation of vascular tissue around the semipermeable membrane is a positive feature because of the close contact between the islets and the circulation, providing a much higher availability of oxygen and nutrients.

The DSPB research team has developed a membrane based on polyelectrolyte complexity with a defined threshold of permeability (so-called molecular weight cutoff) that has an acceptable biocompatibility. The complex infrastructure of research requires comprehension of the molecular and chemical characteristics of polymers, the continuous process of microcapsule preparation in sterile conditions, chemical and mechanical stability of microcapsules and their permeability, specific composition, and immunohistochemical surface after explantation (**Figure 3**). These tasks are performed in cooperation with the Chicago Project (www.thechicagoproject.org), with its goal being to provide an effective treatment for diabetes by 2010. Under the terms of cooperation, thousands of human pancreatic islets are transported from the University of Illinois to the DSPB of the Slovak Academy of Science, where they are encapsulated and then returned to Chicago. Part of the biological material is retained in Slovakia for local studies, which also contribute to the Chicago Project. This scientific research may also demonstrate the possibility of transporting pancreatic islets with retention of their viability and transplantation potential. This is an example of how international research collaboration can work between continents.

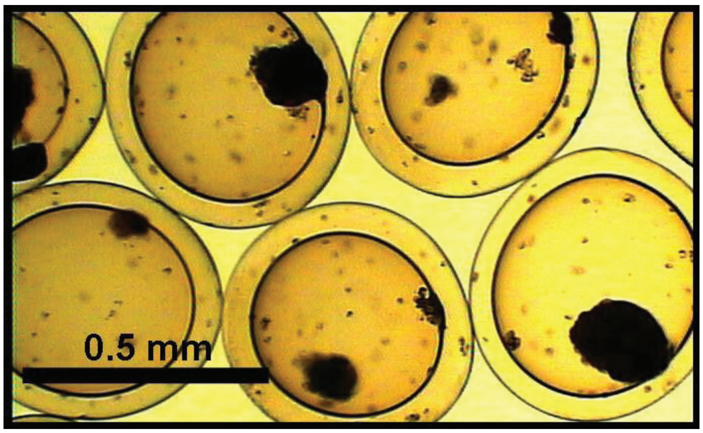

Figure 3. Microcapsules based on polyelectrolyte complexation with encapsulated human islets of Langerhans (from Igor Lacik of the Slovak Academia of Science).

The DSPB Slovak group is a member of the Bioencapsulation Research Group (www.bioencapsulation.net) within the EU-COST project (cost865.bioencapsulation.net). To maintain consistency of the properties of bioartificial organs, this group promotes interlaboratory comparisons of data obtained with different materials and protocols to establish consistency in islet encapsulation data. The experience obtained with the development of biocompatible encapsulation technology at the Slovak Academy of Science has been applied in the development of continuous implantable monitoring systems for diabetic patients.[10] This work is being performed within the 6th Framework Project of European Union: "Integration of nano-biology to provide a continuous care and implantable monitoring system for diabetic patients" (www.p-cezanne.eu). The most recent advances place the bioartificial pancreas in one of the most promising and rapidly advancing areas of research. Current challenges, including attempts to surmount the technological and biological limitations, notwithstanding ethical, political, and regulatory obstacles, must be overcome if the promise of cell encapsulation technology is to be realized in the treatment of human diabetes.

The three described areas appear to be important and motivating for the further development of diabetes treatment.

References:

1. Mignault D, St-Onge M, Karelis AS, Allison DB, Rabsa-Lhoret R. Evaluation of the Portable Healthwear Armband: a device to measure total daily energy expenditure in free-living type 2 diabetic individuals. Diabetes Care. 2005 Jan;28(1):225-7.
2. Jakicic JM, Marcus M, Gallagher KI, Randall C, Thomas E, Goss FL, Robertson RJ. Evaluation of the SenseWear Pro Armand to assess energy expenditure during exercise. Med Sci Sports Exerc. 2004 May;36(5):897-904.
3. De Cristofaro P, Pietrobelli A, Dragani B, Maltesta G, Arzeni S. Total energy expenditure in morbidly obese subjects: a new device validation. Obesity Res. 2005;13:A175.
4. Kronholm E, Aunola S, Hyyppa MT, Kaitsaari M, Koskenvuo M, Mattlar CE, Ronnemaa T. Sleep in monozygotic twins pairs discordant for obesity. J Appl Physiol. 1996 Jan;80(1):14-9.
5. Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E. Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. J Appl Physiol. 2005 Nov;99(5):2008-19.
6. Friedlander A. Sleep apnoea linked to increased diabetes risk. Oral Maxillofacial Surg. 1999;6:11-28.
7. Resnick HE, Redline S, Shahar E, Gilpin A, Newman A, Walter R, Ewy GA, Howard BV, Punjabi NM; Sleep Heart Health Study. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. Diabetes Care. 2003 Mar;26(3):702-9.
8. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnoea is independently associated with insulin resistance. Am J Respir Crit Care Med. 2002 Mar 1;165(5):670-6.
9. Pallayova M, Donicova V, Donic V. Association between nocturnal hyperglycaemia and severe sleep-disordered breathing in type 2 diabetic patients: a study based on continuous glucose monitoring. Diabetologia. 2006;49(suppl. 1):152.
10. Harsch IA, Schahin SP, Radespiel-Troger M, Weintz O, Jahreiss H, Fuchs FS, Wiest GH, Hahn EG, Lohmann T, Konturek PC, Ficker JH. Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnoea syndrome. Am J Respir Crit Care Med. 2004 Jan 15;169(2):156-62.
11. Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T. Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. Arch Intern Med. 2005 Feb 28;165(4):447-52.
12. Chang TMS. Semipermeable microcapsules. Science. 1964 Oct;146(3643):524-5.
13. Korec R. Experimental and spontaneous diabetes mellitus in the rat and mouse. 2nd ed. Edition Center of University PJ Safarik, Kosice; 1991.