Nowadays diabetes is reaching epidemiological sizes—worldwide the number of diseased is reaching over 197 million people and is constantly rising, thus constituting a serious threat to society. Therefore, finding a way to overcome the disease or to improve the quality of life of diabetic patients is becoming a challenge for many research groups in the world. The Chicago Diabetic Project is the first research project involving world-wide experts with various expertise and from different continents, whose shared aim is to find a functional cure for diabetes. Who was the initiator of this project? What is the leading principle of the project and what are the sources of its financing? How many research facilities and researchers are involved in this project?

The cornerstone of The Chicago Diabetes Project, as an academic and non-for-profit effort with the goal to cure diabetes, was laid at the end of year 2004 by the meeting sponsored by the initiators of the project The University of Illinois at Chicago and The Washington Square Health Foundation. The project leader, Prof. José Oberholzer, the Director for Cell and Pancreas Transplantation and the Cell Isolation Laboratory, invited to Chicago the world-experts from diverse scientific fields related to clinical and basic diabetes research to discuss the current situation and to propose the steps that would lead to the functional cure for diabetes.

The functional cure for diabetes was decided to be based on the current level of understanding related to the function of pancreatic insulin-producing cells (islets of Langerhans) in a healthy human, to the pathways of their damage in a diabetic patient as well as to the proven concept that the islet transplantation can become a reality in diabetes treatment. The small number of human pancreatic islets available for transplantation and the need for their continuous protection from the immune system were seen as the major hurdles to be overcome.

The aim The Chicago Diabetes Project is to identify an unlimited source of the insulin-producing cells that will be suitable for safe transplantation to humans and capable to control the blood glucose levels. The need for the immunosuppressive drugs is avoided by encapsulation of these cells in a semi-permeable membrane that protects them against the attack by the immune system and enables a free passage of nutrients, glucose and insulin.

The project is complex and, therefore, it is demanding in terms of expertise as well as funding. The work carried out within The Chicago Diabetes Project is funded from various resources. Currently, a significant portion of the funding is based on the philanthropic contribution from the individuals so far mainly from the Chicago region. In addition, the members of the project are continuously preparing proposals to various national and international funding agencies to organize the additional funding. Regarding the number of research groups and expertise, this has been developing since the project initiation and currently The Chicago Diabetes Project involves tens of researcher teams from United States (University of Illinois at Chicago, University of Illinois at Urbana-Champaign, The Johns Hopkins University Baltimore, Cleveland Clinic), Europe (University of Trondheim, Norway, University of Lille, France, Polymer Institute of the Slovak Academy of Sciences in Bratislava, Slovakia, Switzerland, Aqua+Tech Specialties, Switzerland) and Australia (Australian Foundation for Diabetes Research, Sydney).

What were the selection criteria for the project’s participants? Were the personal achievements or the university’s prestige the deciding factors, or was there some other criterion? Specialists of which branches take part in the studies?

The selection criteria followed the need of The Chicago Diabetes Project to fulfill the principal goals. In principle, Prof. Oberholzer contacted most of the leading groups around the world. Currently several teams work on the identification of new sources of the insulin-producing cells (University of Illinois at Chicago, The Johns Hopkins University, University of Lille, Geneva School of Medicine) and, in parallel, several teams work on finding the most suitable encapsulation technology (Polymer Institute, University of Trondheim, Australian Foundation for Diabetes Research, Aqua+Tech Specialties, University of Illinois at Urbana-Champaign). These activities are closely associated with the activities of the University of Illinois at Chicago, as the central institution of The Chicago Diabetes Project, which works on islet isolation from human donors as well as various animals for the pre-clinical validation aiming at the clinical trials. More information can be found on the web page of the project (www.chicagodiabetesproject.org).

It needs to be pointed out that one of the criteria was the condition of an unrestricted communication among the participating institutions for the effective exchange of information in order to find the answers to the questions in the most effective way. This principle of the cooperation within The Chicago Diabetes Project has been providing the outcomes at much faster way than is typically seen in case of smaller projects among a few institution organized in a competitive way.

We congratulate on being included in such an elite group. What is your experience in studies over diabetes? How did you become involved in this project? How large is the group of researchers involved in the realization of the project? Is this your first experience of working in an international team?
My experience with studies of diabetes started in the middle of 1990-ties during my post-doctoral stay at Vanderbilt University, Nashville, TN. As a polymer chemist dealing with various aspects of water-soluble polymers, I was invited by Prof. Taylor Wang to join his team working on microencapsulation of islets of Langerhans for diabetes treatment. This was the time when the first clinical trial was announced and, consequently, there was a strong development in this area. I was responsible for the design of semipermeable membrane in a form of microcapsules (diameter of ~700 μm) for islet encapsulation which were based on the polyelectrolyte complexation process. These studies resulted in novel microcapsules as well as the development of the continuous encapsulation process. Both these achievements were patented.

After my return to Slovakia, I succeeded to create the infrastructure at the Polymer Institute of the Slovak Academy of Sciences in Bratislava to study the problems at the boundary of polymer chemistry and application of microencapsulation technology in biomedicine and biotechnology. In 2004 my team was invited to join The Chicago Diabetes Project.

We are having the opportunity to be in contact with the peers in the field also in other international projects. Among others, we have been cooperating with University of Göttingen, BASF SE in Ludwigshafen and Queens University in Kingston on the kinetics and mechanism of polymerization of water-soluble monomers. In the last four years we have a very broad international collaboration within the EU-funded Integrated project P. Cezanne with the aim to develop an implantable glucose biosensor. However, the participation on The Chicago Diabetes Project has been one of the most significant experiences in my professional life as well as for my team. We have a chance to answer the crucial questions on diabetes treatment by encapsulation of the insulin-producing cells and to help the diabetic patients to provide them the functional cure.

**Which part of the studies are you participating in? What studies are you responsible for?**

Our role is to provide to The Chicago Diabetes Project the microencapsulation technology with the vision that it will be possible to be used in the clinical trials. This main goal consists of numerous particular tasks sketched briefly below.

For the project we proposed the polymeric microcapsules developed during my stay at Vanderbilt University, which were subjected to several optimization steps in terms of recipe and encapsulation protocol. The microcapsule development is connected with a thorough characterization of physicochemical properties such as permeability to quantify the semipermeable character of the membrane, and chemical and mechanical stability in culture media to correlate the resistance of microcapsules to the environment after their transplantation. Then the microcapsules are used for sterile encapsulation of islets of Langerhans from various donors (animal and human islets). Various staining strategies are employed to characterize the effect of encapsulation on islets viability and the release of insulin as a response to various levels of glucose concentrations. In parallel to these in vitro tests, the microcapsules are tested in vivo. The peritoneal cavity is the most common site of transplantation of microcapsules. First the empty capsules are transplanted to recognize their biocompatibility. The surface of microcapsules cannot be overlaid by the fibrotic tissue that would cause the diffusion barrier of glucose and nutrients to encapsulated islets and, eventually, the death of islets and transplant failure. In case when the empty microcapsules are tolerated by the immune system of the recipient, the microcapsules are used for encapsulation of islets and their transplantation to the diabetic animal models. The in vivo studies thus show the level of biocompatibility and the ability of encapsulated islets to reverse diabetes.

Tens of optimization steps were performed until we arrived to both the microcapsule composition and the microencapsulation process that are currently used in The Chicago Diabetes Project. In addition to the rodent animal models, the last year transplantations to baboons, as the non-human primate animal model, make us to believe that this microcapsule is a strong candidate for the preclinical validation with the perspective to be used in the clinical trials.

In addition to this main stream of activities we are responsible for physicochemical testing of all microcapsules, which have been used in the project. In order to compare the characteristics of various microcapsules prepared by other teams and to correlate them with the in vivo performance, the comparative tests carried out by a single laboratory is very important and was missing in the past.

The idea of the project is to use pancreatic cells which produce insulin in therapy for diabetic patients. The first step was their isolation. What does it involve? What happens to them later? What are the next stages of the work? What role in the studies is played by polymer chemistry and how important is it?

Currently The Chicago Diabetes Project is following the strategy of testing the microcapsules with allotransplanted islets of Langerhans, i.e. in the first stage to show the functional cure of diabetes in human patients with human islets of Langerhans. In the second stage, the derived cells of human origin from other sources than pancreas will be encapsulated after they will become available. It should be mentioned at this point that other teams around the world in the search for the unlimited source of insulin-producing cells have proposed xenotransplantation of microencapsulated porcine islets of Langerhans. For example, recently clinical trials were initiated by the New Zealand-based company Living Cell Technology, Inc. This approach may represent some safety risks to the patient, which judgment is obviously outside of my expertise. On the other hand, these trials support the principle of the islet microencapsulation technology as a feasible strategy for functional cure of diabetes in human patients.

The team at the University of Illinois at Chicago belongs to the top teams in the United States in terms of human islets isolation and transplantation by so called Edmonton protocol, where the isolated free (non-encapsulated) human islets of Langerhans are transplanted to the liver. This protocol, however, involves the immunosuppressive drugs that need to be administered to the patient to avoid the rejection of islets by the immune system. Apart from the glucose level control for, in average, about one year, the side effects often occur as a consequence of the administration of immunosuppressive drugs.

A few months ago, during my last visit at the University of Illinois, I had a chance to be at the islet isolation from human pancreas. The pancreas is digested by an enzyme in a controlled way that the intact islets are separated from the pancreas exocrine tissue. This is extremely precise, delicate and hard process usually carried out during the night hours and requires the coordinated team of well-trained specialists. The islets are characterized in terms of purity, viability and glucose stimulation and are cultured until they are further processed. The microencapsulation must be carried out in such a way that the viability of islets is not reduced.

**How long do the cells implanted in the patient fulfill their task? Are these cells attacked by the patient’s autoimmune system? To what degree does this constitute an obstacle/limitation in using this method? How does this method differ from other controlled drug-releasing systems currently popularized in world-wide scientific trends?**

The current animal studies prove that the encapsulated islets of
The microencapsulation of islets of Langerhans represents the cell-based therapy where the attack by the recipient's immune system should be suppressed to the minimum. The premise of this therapy is to keep the microencapsulated cells viable and functional for as long as possible. The microencapsulated islets of Langerhans function after transplantation in the same way as the artificial pancreas: they release the required amount of insulin depending on the actual glucose level in the islet environment. This "active" control of the missing hormone to be delivered to the organism differs to that used in other controlled drug-releasing systems, which are often determined by dissolution and/or degradation of the matrix or other means for targeted delivery of a drug. Specifically for the insulin delivery, currently there is no another such precise possibility to deliver insulin to the diabetic patient that the glucose levels are continuously as close as possible to the physiological values.

What decides about the innovation of such approach to the way of treating diabetes? How much chemistry, medicine and pharmacy does it include – can the percentage ratio of these sciences in the realization of such treatment manner be determined? What are the benefits and threats?

The diabetes treatment by microencapsulated islets of Langerhans can be considered as a typical field where polymer-based materials are applied to help the human health. This field has gone through the excitement as well as the depression periods, with a lot investment and promises made throughout its almost 30 years of history. There exist several proofs-of-principle and our task within The Chicago Diabetes Project is to arrive to the microencapsulation technology generally applicable to a large population of diabetic patients. Therefore the leading lines are safety of microcapsules as the implanted biomaterial and long-term functionality of the microencapsulated islets after their transplantation. We understand that the high qualities of both microcapsules and insulin-producing cells have to meet in order to succeed in this project. All the activities from the areas of chemistry, medicine and pharmacy leading to this goal are highly complementary and it is hard to judge their significance to get to the ultimate goal. In principle, if one of them is not at its optimum, the final result will most likely be the failure. As mentioned before, if we succeed the benefits for the diabetic patient will be enormous in terms of quality of life and eliminating the fear from the diabetic complications. Another benefit is that this therapy does not require the presence of immunosuppressive drugs. This enhances the safety of this approach. It even may allow for applying this therapy to diabetic children, which says that the associated risks should indeed be negligible.

Are the researchers involved in the Chicago Diabetic Project close to achieving their aim? What constitutes the biggest problem for them? What is the work organization of groups from different research facilities in various countries? Describe the manner of information exchange and planning further works.

The aim of this stage is to show that the current microencapsulation technology is suitable for entering the clinical trials. I would like to notify that the data obtained from clinical transplantation of free islets by the Edmonton protocol mentioned above. After the encapsulated islets lose their function, the microcapsules are expected to be explanted and fresh microencapsulated islets will be transplanted to control the blood glucose levels.

Do the studies conducted as part of the Chicago Diabetic Project include pharmaceutical companies? Does the project anticipate cooperation with pharmaceutical companies already at the production stage? How will the worked-out therapy be popularized among patients? To what degree will the treatment of diabetes via this method be available?

The Chicago Diabetes Project is publicly open project with the goal to effectively show whether the undertaken strategy can represent the ultimate functional cure for diabetes. The project has been profiting from the freedom and non-restricted sharing of information among the involved institutions that would be difficult if the project is already roofed by pharmaceutical or another company. In case we succeed in the clinical trials, the specialists will be approached to make this technology available for wide population of diabetic patients.

In your opinion, to what extent will the results of this project contribute to improving the quality of life of people with diabetes?

I have been in contact with many diabetic patients and diabetes type I is unfortunately also influencing my close relatives. I can realize how difficult it may be to organize the everyday life that the glucose levels do not deviate significantly from the physiological values. I have also had a chance to talk to the diabetic patients who were transplanted with free islets of Langerhans by Prof. Oberholzer at the University of Illinois. These were the patients who were suffering from uncontrolled hypoglycemic events, which could come anytime. They were describing how was their quality of life before the transplantation with the fear that this day may be the last one in case that the hypoglycemia suddenly comes, for example, during driving. And how the life changed after the transplanted islets started to control the blood glucose. This needs no further arguments.

Many studies and certainly many achievements have been made in terms of controlling the blood glucose levels by for example continuous glucose monitoring systems that include glucose sensor connected in a sophisticated way to the insulin infusion pump. Nevertheless, the insulin-producing cells is naturally the most precise sensor and the insulin pump for controlling the physiological levels of insulin, and hence glucose. The Chicago Diabetes Project team believes that their microencapsulation in the polymeric microcapsules represents the premise for the functional cure of diabetes.

Thank you very much for the conversation. Once again, I congratulate you on your participation in this outstanding project. CHEMIK recommends its pages for presenting the results of this and other projects connected with chemistry in pharmacy.

interview by Maria Jamroz-Piegza