Development of a Novel Osmotic-Pressure-based implantable glucose sensor technology for long-term use in patients with diabetes

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Regular measurement of blood glucose is a mandatory task for insulin treated people with type 1 and type 2 diabetes, and is currently considered to be the most painful procedure during daily routine care.[1,2]

The development of pain-free methods for the assessment of the glucose information for treatment orchestration for patients with diabetes mellitus has been the goal of many academic and commercial technology research groups for decades. Despite major efforts in time, funding and human resources, only few products with moderate to acceptable performance have come close to or have even reached the market yet.[3-5] An implantable glucose sensor for use for up to 3 months has recently been introduced to the market, which however requires still two invasive calibration measurements per day for acceptable accuracy.[6]

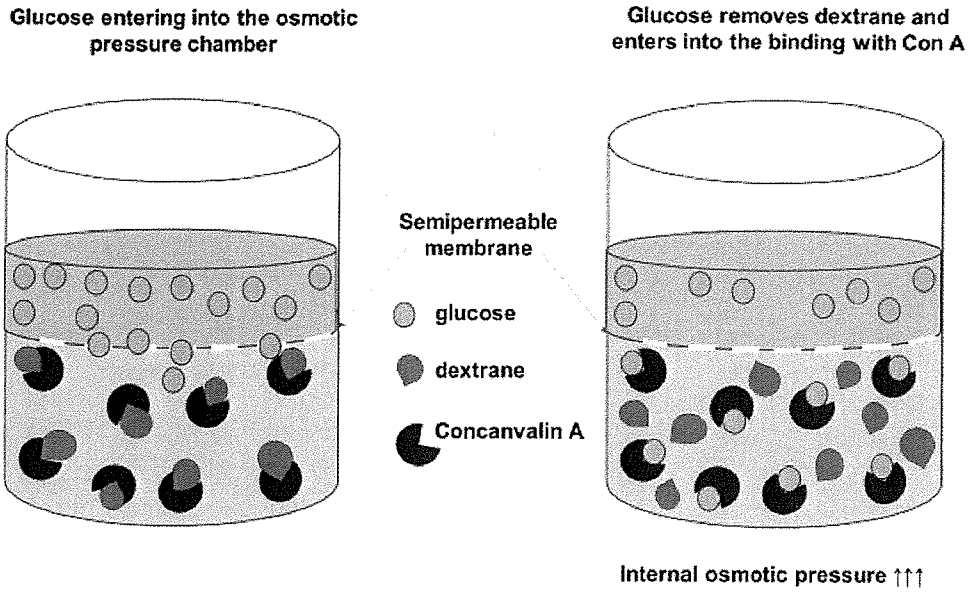
The Technology

A novel implantable glucose affinity biosensor (Sencell, LifeCare, Norway) is currently under development, which is based on the competitive and reversible binding of glucose and the polysaccharide dextrane to the glucose specific lectin concavalin A (ConA). The proprietary Sencell technology uses osmotic pressure differences arising between a reagent chamber (containing active fluid with ConA and dextrane) and a diffusion chamber (in direct contact with interstitial fluid) to determine interstitial glucose concentrations. Both compartments are separated by a nanoporous membrane permeable to glucose and water, but not to ConA or dextrane (see Figure 1).

Once glucose concentrations rise in the interstitial fluid, glucose will diffuse through the membrane and will remove the dextrane from the ConA binding sites because of higher affinity. This process results in an increase in osmotic pressure because both ConA and dextrane are also independently osmotically active on their own. Detailed descriptions of the underlying technology have been published previously, showing a dynamic glucose range of laboratory prototypes of 36 – 720 mg/dL with a sensitivity of 2.3 mg/dL.[7-9]

One key advantage of this novel sensing technology, which differentiates it from other glucose measurement technologies, is that the chemical glucose concentration is translated into a physical pressure signal without consuming or destroying the glucose mo- →

Figure 1
Working principle of an osmotic-pressure based glucose sensor



lecule. The longevity of the sensor operations may therefore only be limited by biological reactions of the body, but not by the underlying measurement technology. It is therefore anticipated that the final sensor may operate at least for 6 months and longer in the individual patient.

The osmotic effect from the physiological levels of several key metabolites and nutritional components has been investigated in vitro, showing potential interference from only very few molecules, in particular ethanol, lactate and free amino acids. In these studies, mannose and ascorbic acid were also identified as potentially interfering substances, but their physiological concentrations in the interstitial fluid are far too low to have any measurable impact on the ConA-dextrane affinity assay and can be neglected *in vivo*.[10]

Preclinical Results

A first study in three pigs performed with a crude wired version of the first sensor generation (a disk with a diameter of 3 cm and a height of 0.6 cm) demonstrated the capability of the technology to track interstitial glucose and served as a proof-of-concept confirmation. After some mathematical processing in line with algorithms employed also in commercial continuous glucose monitoring systems, and after performing a retrospective calibration, the Sencell signals showed good agreement with the Dexcom G4 comparator results. This preliminary preclinical trial also led to specific sensor modifications for signal noise reduction, e.g. the introduction of a second measurement reference chamber without ConA to measure mechanical pressure noise signals and deduct them from the signals of the glucose sensor.[11]

This device iteration was evaluated in another animal experiment, again performed with wired prototypes (1.5 x 2.0 x 0.5 cm^3). Implantation of four modified Sencell sensors and one Dexcom® G4 control sensor was performed in the back and the neck area of three pigs (1 female, 2 male), respectively. After two days of equilibration and signal documentation, they received an i.v. glucose load of up to 100 mg/kg of dextrose. Reference measurements from capillary blood samples were performed using the YSI 2300 STAT Plus glucose analyser every 15 min for 5 h. Several Sencell prototype devices were able to track glucose changes paralleling the results of the Dexcom Sensor over extended time periods.

In comparison to the previous results, deduction of movement artefacts as captured by the reference pressure chamber, substantially reduced the noise level of the signals. The magnitude of the signals

was in a predicted range and working sensors were matching G4 results. Although the body temperatures in the animals within three experimental days partially exceeded 39°C, the activity of ConA was preserved. No external signs of inflammation were observed in the histology examinations. In conclusion, improved performance of the actual sensor after recent design modification could be demonstrated *in vivo*.[12]

The next development steps

The next step of the development is driven by a substantial further device miniaturization. The plan is to reduce the size to (0.5 x 0.5 x 2 mm), to make the sensor injectable by means of commercially available injection needles. In order to achieve such a small overall size for the entire sensing element and the additional energy induction and data transfer components, methods of nanotechnology will be employed. When reducing the size of the osmotic pressure chamber to meet the planned specifications, an ultrasensitive pressure transducer will be required. A 3D-nanoprinting method will be used to manufacture ultra-small pressure sensors with a sufficiently high signal sensitivity. The underlying physical and chemical characteristics of these nano-sensors have been published recently.[13]

By employing such means of nanotechnology, it will be possible to even use several osmotic pressure sensors in one device, which will allow for collection of several redundant signals and may positively impact the longevity of the implanted device. The read-out device, which will also be used to induce the operational energy in the sensor may be operated as part of a wrist watch or a mobile phone. It is also considered to have insulin pumps equipped with a read-out capability for the Sencell sensor and to thus make it become the sensing part of an artificial pancreas system. ■

CONCLUSION

The development of a very small injectable sensor for assessment of interstitial glucose information is well on its way. The sensor can be used for at least 6 month and provides access to an unlimited number of pain-free glucose readings. This device may help to improve glycemic control and to reduce incidence and progression of secondary complications.

Disclosures
Rune Frisvold is employee and shareholder of Lifecare AS the developer of the Sencell device.
Andreas Pfützner and Kåre Birkland work as consultants and have received consulting fees and travel support from Lifecare.
Sanja Ramljak has no conflict of interest to disclose.

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