

DEVELOPMENT OF AN IMPLANTABLE GLUCOSE SENSOR

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EXECUTIVE SUMMARY

Diabetes takes an enormous toll both on the individual and society. However, accurate monitoring of blood glucose levels when combined with insulin therapy dramatically improves upon lifestyle and lifespan. Unfortunately, the current gold standard method for blood glucose measurement requires an invasive test. The purpose of this project is to develop an implantable, externally readable glucose sensor. The specific technical challenges that must be met for the successful development of a functional, *in vivo* glucose sensor are: a self-contained glucose sensing system; interfaced with an electronics compatible signal transduction unit; contained in a biostable device with a biocompatible interface. Numerous previous attempts to build a commercially viable implantable glucose sensor have failed due to weaknesses in all three of these critical components. Failure examples include: external reagent or renewable materials requirements, device size and limited communication capabilities and adverse interactions with the biological system. It is our goal to overcome these traditional challenges to build the first successful, *in vivo* glucose sensor. Our strategy for success is based on three key observations: the glucose sensing system must be built from selective, stable and self-contained components that reversibly respond to glucose concentration; the signal transduction and communication electronics must be limited to the millimeter size scale; and the biostable system must include protection of the sensing system from biochemical interference while also maintaining permeability (that is, correlation to glucose concentration) in the long term. Our design will individually and collectively solve these problems by combining RECEPTORS' AFFINITY by DESIGN™ platform with Digital Angels' and VeriChip's *in vivo* and RFID technology.

OPPORTUNITY

Diabetes is one of the leading causes of morbidity and mortality. In addition to quality of life issues, diabetes takes an enormous economic toll both on the individual and on society. Although diabetes is presently not curable, accurate monitoring of blood glucose levels when combined with insulin therapy dramatically improves on both lifestyle and lifespan. Unfortunately, the current gold standard method for blood glucose measurement requires a sample of blood; an invasive test. Over the long-term, the

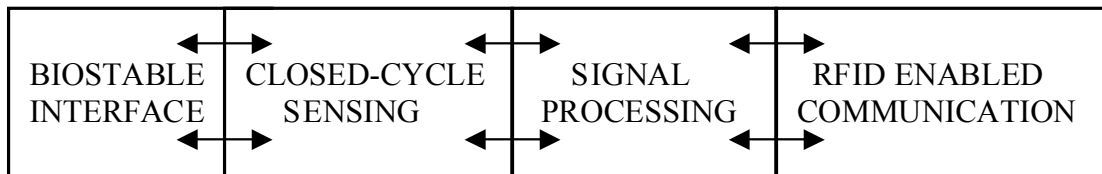
requirement that the diabetic must prick their finger multiple times a day for a blood sample leads to less than ideal measurement frequency and, as a result, out of range blood glucose levels. Clearly, there is both a dramatic societal need and significant economic benefit to be gained from an easy to use, implantable glucose measurement system.

Over the past several decades, there have been numerous efforts to build a successful *in vivo* glucose sensor. None of these efforts have been successful due to external reagent or renewable materials requirements, device size and limited communication capabilities and adverse interactions with the biological system and/or some combination of all of these failure modes. Our program will overcome these roadblocks through the development of a stable, self-contained glucose sensing system that is contained in a selectively porous, biocompatible membrane. This biostable sensing component will be incorporated into a millimeter scale signal transduction and RFID enabled communication device.

STRATEGY

The development of an *in vivo* glucose sensor has proven to be problematic because of the failure to effectively integrate the critical biocompatible interface, glucose sensing system, glucose-to-signal transducer and communication components. The fundamental flaw in these previous approaches has been the lack of component integration during the design process. Successful development of one component has typically led to an ad hoc approach to integration of the entire system. Our approach is based on an in-depth consideration of all of the critical components and development of a strategy that is based on the requirements of each component relative to the system as a whole (FIGURE 1). The key components of our approach are the bioselective interface between the *in vivo* environment and the sensing system, the closed-cycle glucose sensing system and a mass sensitive glucose-to-signal transduction interface that is coupled to the RFID enabled data communication component.

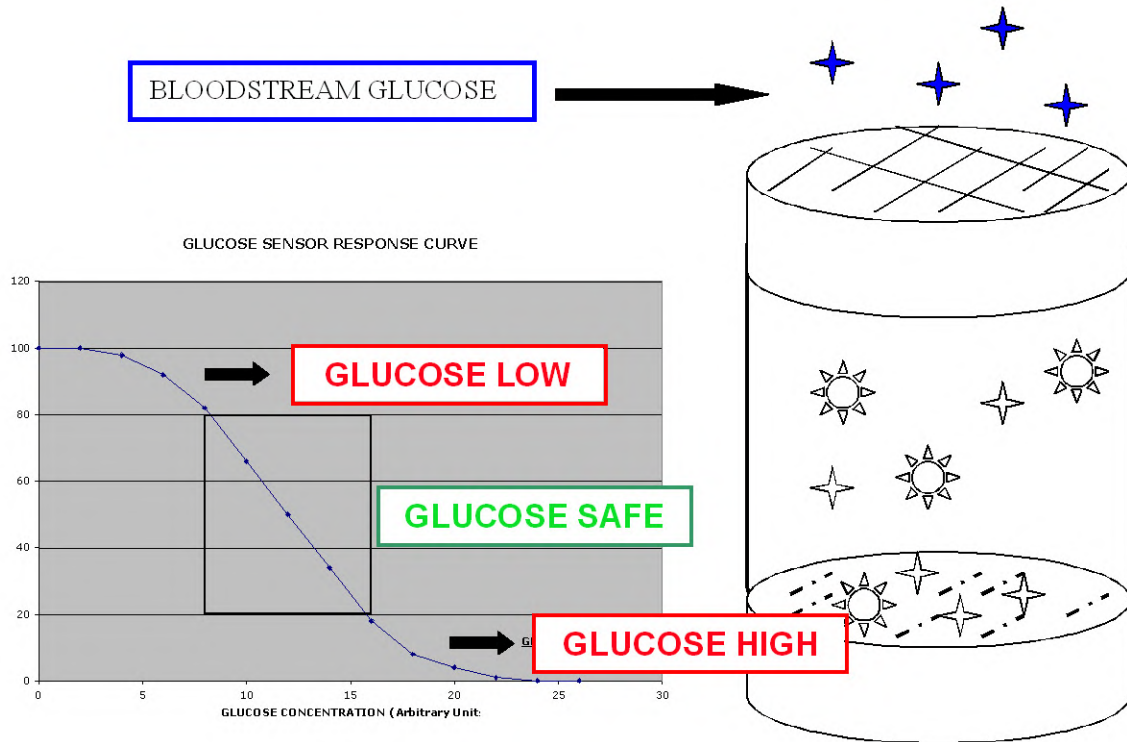
FIGURE 1. CRITICAL COMPONENTS SCHEMATIC.



PROJECT PLAN OVERVIEW

The design of the device is based on the creation of an integrated unit that will produce an RFID communication read-out of "LOW - SAFE - HIGH" glucose levels (FIGURE 2).

FIGURE 2. GLUCOSE SENSING SYSTEM DESIGN.



Bloodstream glucose levels will produce a proportionate response in the glucose sensing system and, correspondingly, in the electronics to RFID communication read-out.

This project will be divided into FOUR phases (FIGURE 3):

PHASE I

Demonstration of the self-contained glucose sensing system (6 months).

PHASE II

Development of the glucose sensing system / electronics interface (8 months).
Optimization of the electronics interface (3 months).

PHASE III

ASIC / RFID design and development (12 months)
Construction and optimization of the glucose sensing device (7 months).

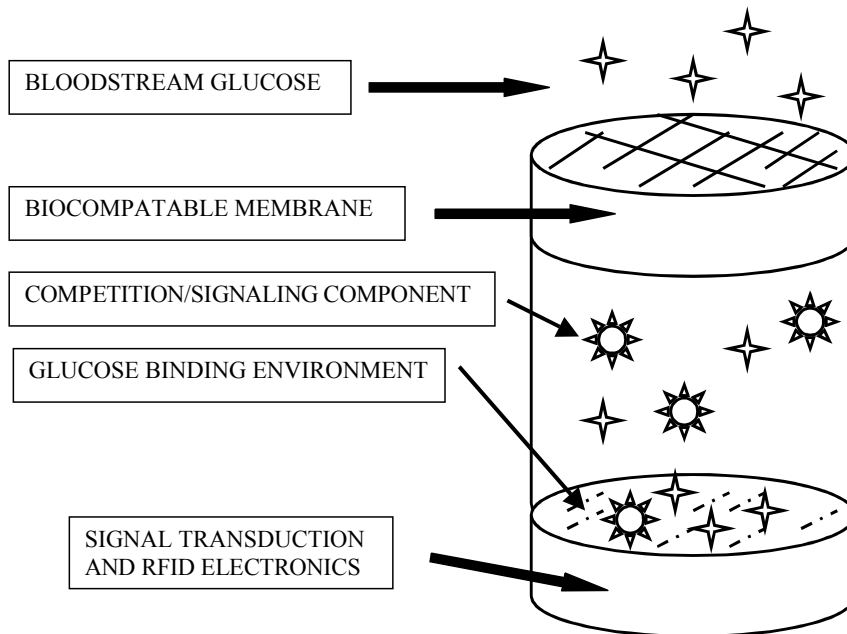
PHASE IV -

Initiate clinical trials (2 months).

TIMELINE: 30 months

FIGURE 3. INTEGRATED SENSOR DEVICE DESIGN.

The critical bioselective and closed-cycle glucose sensing system, mass sensitive glucose-to-signal transduction interface and RFID enabled data communication components will be combined into an integrated, implantable package.



PHASED PROJECT PLAN

PHASE I: SELF-CONTAINED SENSING SYSTEM

Demonstration of the self-contained sensing system requires the combination of a glucose selective binding environment and a labeled competition / signaling component. The competitive interaction of glucose, the binding environment and the competition component will produce a signal that is proportional to glucose concentration. This design and development plan is based on a combination of RECEPTORS' experience in both analytical systems development and artificial receptor technology. **FIGURE 4** illustrates the general flowscheme that is utilized by RECEPTORS to build selective affinity environments for a wide variety of applications. RECEPTORS has successfully used its CARA™ platform to develop targeted affinity supports for a variety of protein and small molecule applications. Specific examples of the applications of RECEPTORS' CARA™ technology include:

Product / Applications

PROTEOME WINDOWS™ Fractionation Supports

Saliva proteome fractionation for biomarker discovery.

Serum proteome fractionation for common protein depletion and biomarker discovery.

AFFINITY SELECT™ Purification Supports

Selective antibody capture from antiserum and culture fluid for reagent and therapeutic antibody purification.

ONE STEP to MALDI™ Affinity Arrays

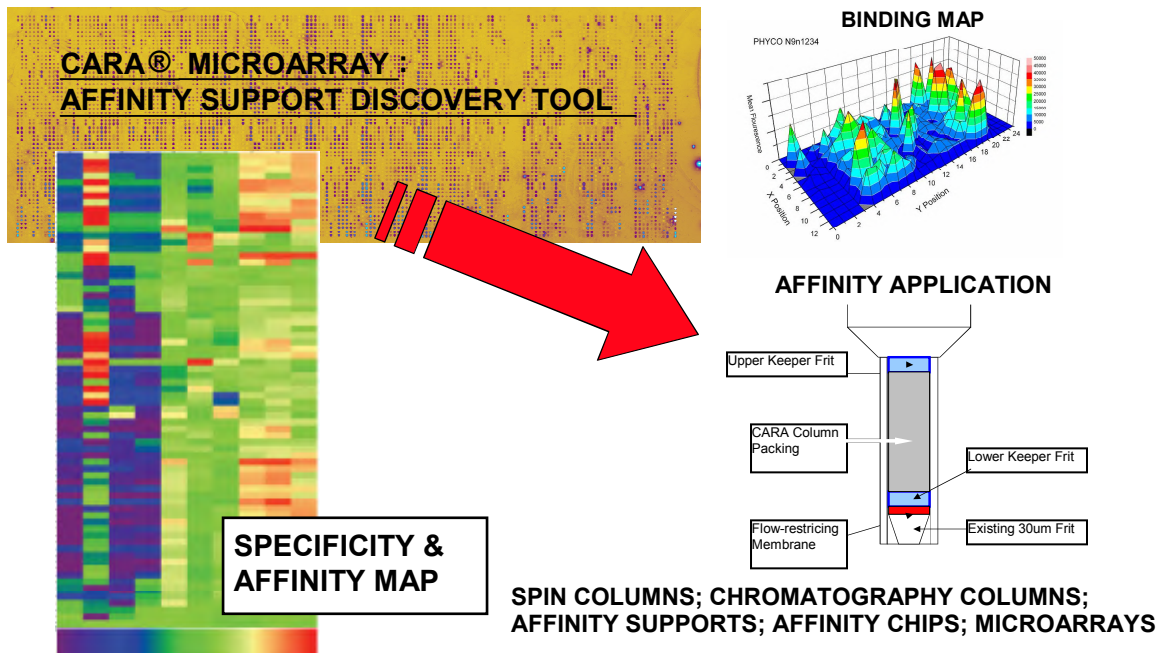
Multiplexed selective affinity capture chip for direct to MALDI biomarker discovery.

MICROBE on TARGET™ Fingerprint Arrays

CARA™ Arrays for the selective affinity detection and identification of pathogenic microbes.

FIGURE 4. AFFINITY APPLIED:

HIGH-THROUGHPUT DISCOVERY FOR OPTIMIZED APPLICATIONS.
RECEPTORS' CARA™ AFFINITY by DESIGN™ Discovery Platform is an efficient tool for the discovery and application of binding environments to any target.

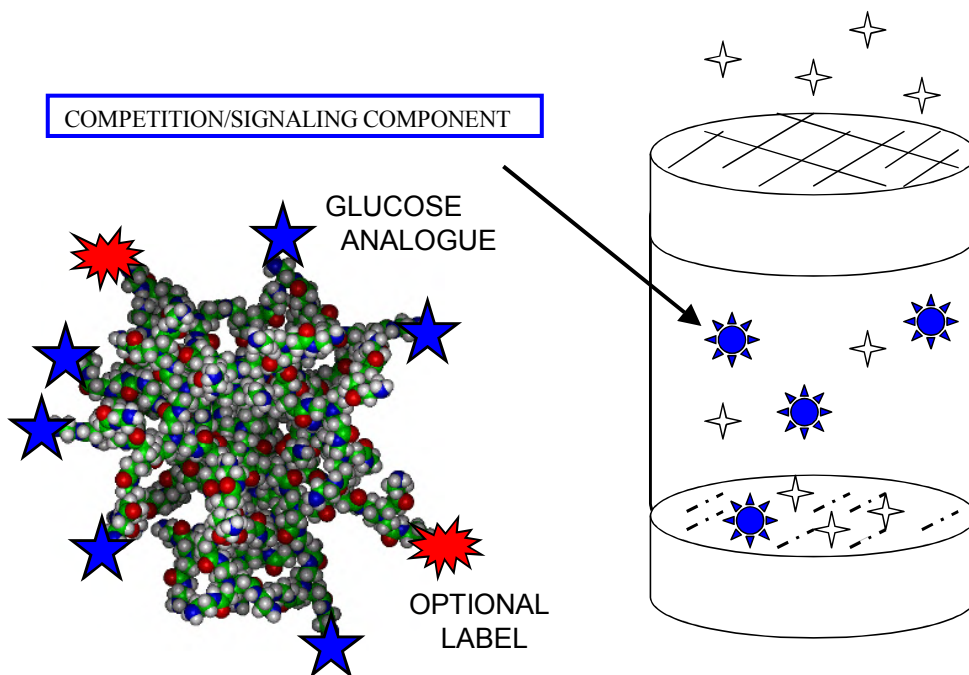


The critical steps in the demonstration of the self-contained glucose sensing system are development of the glucose selective binding environment and a labeled competition / signaling component. The steps in this process, which utilize RECEPTORS' CARA™ workflow and assay competitor expertise, are:

- Combinatorial preparation and high-throughput screen selection of candidate competition/signaling components.
- Microarray based high-throughput screen selection of candidate glucose and competition component binding environments. (FIGURE 5)

FIGURE 5. COMPETITION/SIGNALING COMPONENT

The competition/signaling component will be prepared using a core carrier with glucose analogue moieties. CARA™ microarrays will be used to select the optimum combination of competition component structure and competitor binding environment.



--- Combination and optimization of binding environment and competition/signaling component to demonstrate proportional response to glucose concentration.

--- Optimization of candidate binding environments for sensitivity, specificity and stability.

SEE FIGURE 6

--- Demonstration of the selective molecular weight cut-off, biocompatible membrane based on polymeric, hollow fiber technology.

SEE FIGURE 7

FIGURE 6. OPTIMIZATION OF COMPETITION AND BINDING.

The competition agent and binding environment will be optimized versus glucose concentration and the *in vivo* serum/fluid matrix.

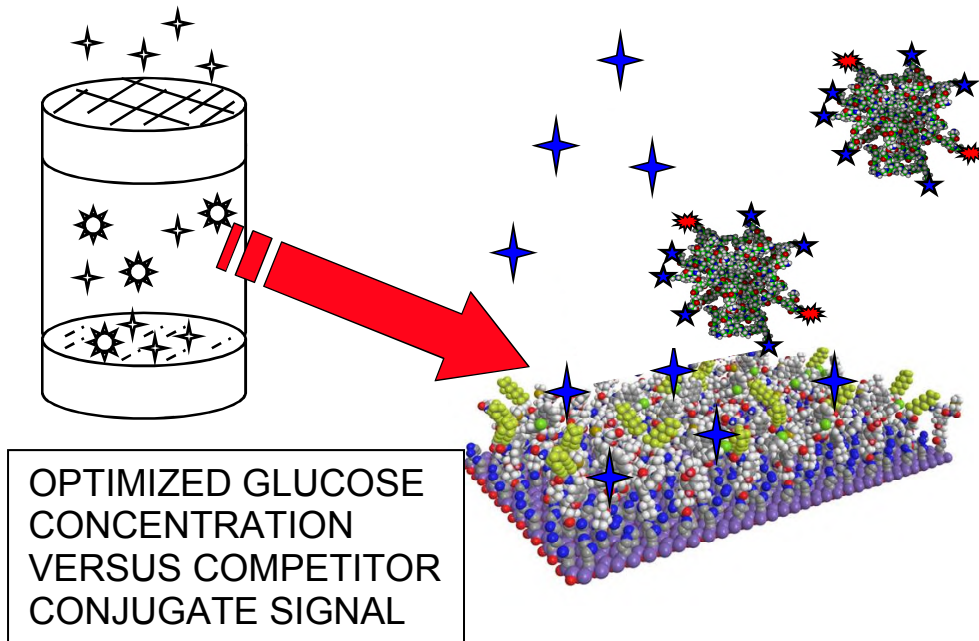
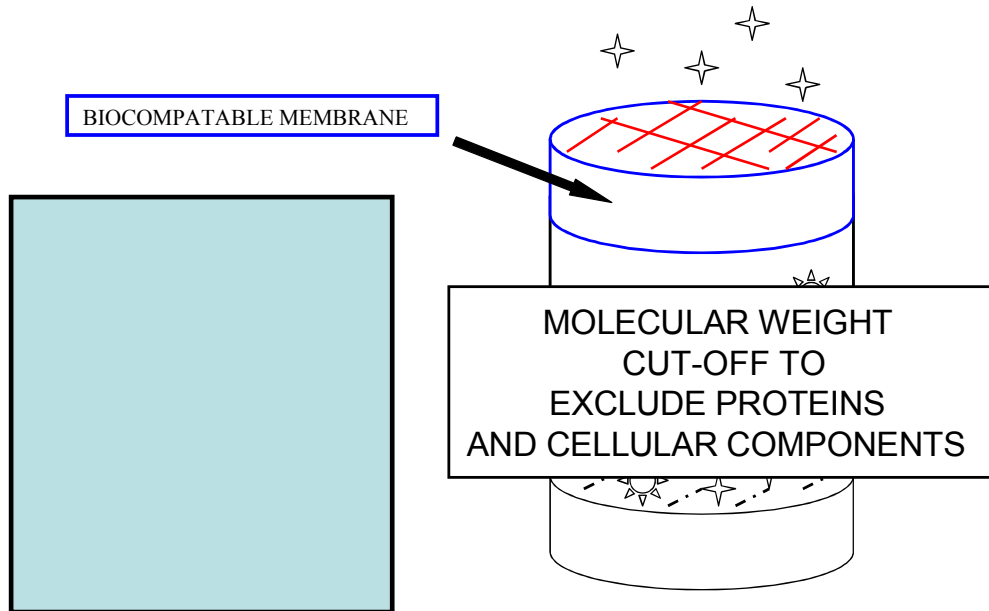


FIGURE 7. EXAMPLE OF BIOCOMPATIBLE HOLLOW-FIBERS.

The hollow fiber matrix will serve the purpose of building the biostable sensing component based on its selectively porous, biocompatible membrane technology as certified versus ISO 10,993-4 evaluation.



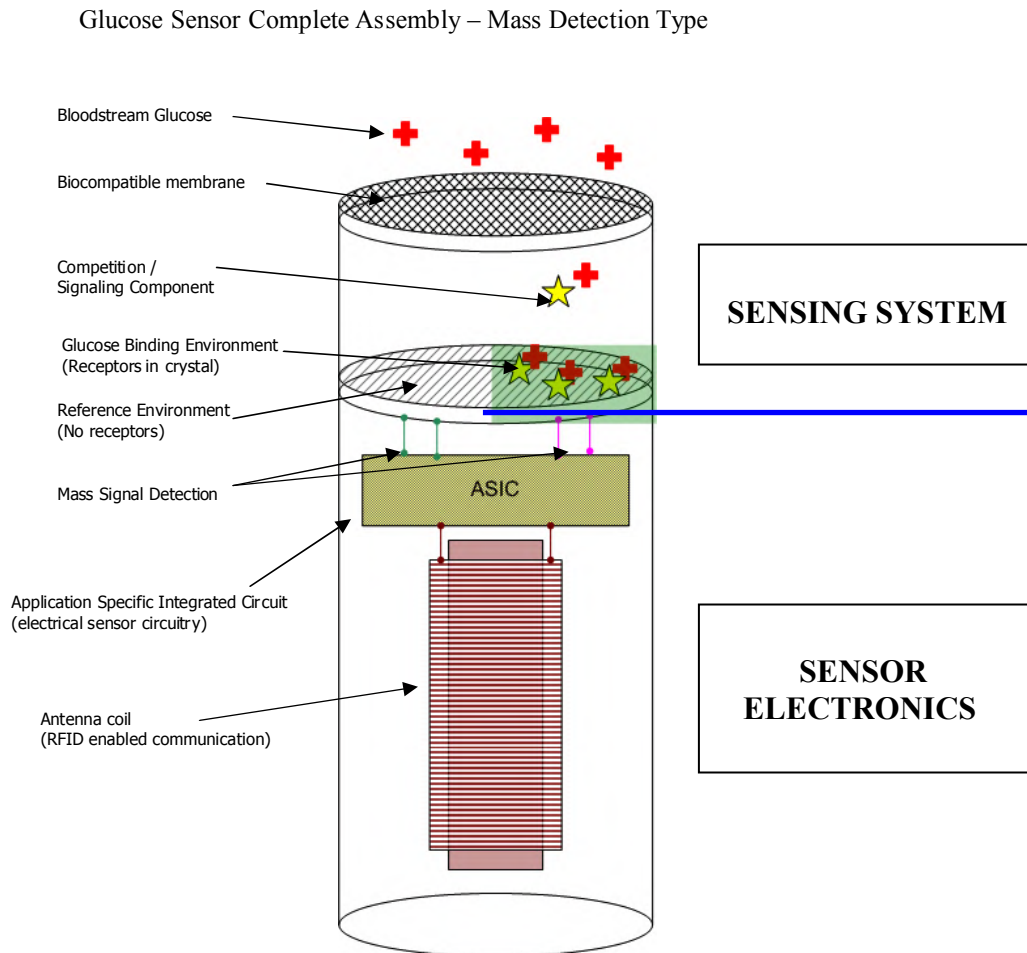
PHASE II: SENSING SYSTEM AND ELECTRONICS INTERFACE.

The sensing system developed in Phase I will provide a mass-to-glucose signal via the competitive binding of the competitor agent versus glucose to the glucose selective binding environment. The mass differential on glucose versus competitor agent binding will be utilized via mass sensitive signal transduction based on frequency resonance detection technology.

PHASE III: GLUCOSE SENSING DEVICE DEVELOPMENT.

The prototype glucose sensor will be produced from the integration of the glucose sensing system with signal transduction based on mass signal detection that is coupled to the application specific, electrical sensor integrated circuitry and the RFID enabled communication electronics (FIGURE 8).

FIGURE 8. COMPONENTS OF THE SENSING / COMMUNICATION DEVICE.



PHASE IV: CLINICAL TRIALS.

Preliminary trials will be designed to review and verify both the sensing system and sensor electronics. This phase of the program will be coordinated with the appropriate clinical trial organizations.

SELECTED REFERENCES

Biomolecule Receptors

-- Nilsson, C. (Ed.), **Lectins: Analytical Technologies**, Elsevier (2007) 456 pp.

Synthetic Receptors

-- Davis, A.P., James, T.D., Carbohydrate Receptors in Schader, T. Hamilton, A.D. (Eds.) **Functional Synthetic Receptors**, Wiley-VCH Verlag GmbH & Co. KGaA (2005) pp.45-109.

-- James, T.D., Phillips, M.D., Shinkai, S., **Boronic Acids in Saccharide Recognition**, Royal Society of Chemistry (2006) 174 pp.

Synthetic Sugar Specific Receptors

-- Edwards, N.Y., et.al., "Boronic Acid Based Peptidic Receptors for Pattern-Based Saccharide Sensing in Neutral Aqueous Media, an Application in Real-life Samples", *Journal of the American Chemical Society*, **129** (2007) p. 13575-13583.

-- Gamsey, S., et.al., "Boronic Acid-based Bipyridinium Salts as Tanable Receptors for Monosaccharides and alpha-Hydroxycarboxylates", *Journal of the American Chemical Society*, **129** (2007) p. 1278-1286.

-- Ferrand, Y., Crump, M.P., Davis, A.P., "A Synthetic Lectin Analog for Biomimetic Disaccharide Recognition", *Science*, **318** (2007) p. 619-622.

RECEPTORS CARA™ Technology

Carlson, R.E., "Artificial Receptors, Building Blocks and Methods", USPTO Published Patent Application #20030203405 (October 30, 2003).

Carlson, R.E., "Sensors Employing Combinatorial Artificial Receptors", USPTO Published Patent Application #20050095698 (May 5, 2005).

Competitor Agent Design

Carlson, R.E., Swanson, T.A., "Immunoassay for Polychlorinated Biphenyls", United States Patent 5,538,852 (July 23, 1996).

Carlson, R.E., "High Sensitivity Immunoassay for Polychlorinated Dibenzo-p-dioxins and Polychlorinated Dibenzofurans", United States Patent 5,674,697 (October 7, 1997).

Sensors

-- Narayanaswamy, R., Wolfbels, O.S. (Eds.), **Optical Sensors: Industrial, Environmental and Diagnostics Applications**, Springer (2004) 421 pp.

Homola, J. (Ed.), **Surface Plasmon Resonance Sensors and Biosensors**, Springer (2006) 251 pp.

In vivo Sensors

- Frost, M.C., Meyerhoff, M.E., "Implantable Chemical Sensors for Real-time Clinical Monitoring: Progress and Challenges", *Current Opinion in Chemical Biology*, **6** (2002) p. 633-641.
- Arnold, M.A., "In Vivo Chemical Sensing - Opportunities and Challenges", *e-biomed: The Journal of Regenerative Medicine*, 1(5), 55-58 (2000).
- Zhou, P., Pang, D., Li, W., "Embedded Bio-Sensor System", US Patent 7,125,382, Oct. 24, 2006.

Biocompatibility

- Abraham, S., et.al., "Molecularly Engineered Hydrogels for Implant Biocompatibility", *Biomaterials*, **26(3)** (2005) p. 4767-4778.
- Frost, M.C., Meyerhoff, M.E., "In Vivo Chemical Sensors: Tackling Biocompatibility", *Analytical Chemistry*, **79** (2006) p. 7370-7377.
- Reynolds, et.al., "Nitric Oxide-Releasing Polyurethane for Biomedical Applications", *Biomacromolecules*, **7**, 987-994 (2006).
- Medtronic, Inc. , "Trillium Biosurface: Triple Endothelial-like Action for Biocompatibility", see http://www.medtronic.com/cardsurgery/arrested_heart/biopassive.html.
- International Organization for Standardization, ISO 10993-4:2002, "Biological Evaluation of Medical Devices - Part 4: Selection of Tests for Interactions with Blood. see <http://www.iso.org>.