# AN INTEGRATED SENSOR SYSTEM FOR THE DETECTION OF BIO-THREATS FROM PANDEMICS TO EMERGING DISEASES TO BIOTERRORISM

WHITE PAPER
07 MAY 2009

Robert E. Carlson, Ph.D.
President and Chief Science Officer
RECEPTORS LLC
Suite 510 / MD 57
1107 Hazeltine Blvd.
Chaska, MN 55318
Voice: 952-448-4337
FAX: 952-448-1651
email: bc@receptorsllc.com
WWW.RECEPTORSLLC.COM

## EXECUTIVE SUMMARY

An integrated system for bio-threat (pandemic, emerging diseases, bioterrorism) detection must include stable, sensitive and selective solutions for the capture and analysis across the diverse spectrum of threat agents. In addition, the ideal threat agent detection and alert system should be capable of both single and multiplexed analysis over the range of toxins, viruses and microbes that present the most significant hazards. However, the products currently in the marketplace fail to provide a comprehensive solution and, most importantly, are not stable or scalable. Moreover, these systems are generally too specific as they are targeted to a particular pathogen strain. Thus, long development and approval cycles result in market introductions that are considerably post-threat and not adaptable to current or emerging threats. There is a clear need for a biothreat sensor system that spans the range from surveillance and early warning of both known and novel agents to multiplexed diagnostics for rapid and broadly applicable classification and characterization during an outbreak event. RECEPTORS' AFFINITY by DESIGN™ CARA™ platform and VeriChip's signal transduction and RFID communication expertise combine capture, analysis, response and report into a stable, scalable and threat selective platform which will be developed into an integrated suite of sensor products that cover the bio-threat/biodefense spectrum.

OPPORTUNITY

Natural and human events combine to produce a steady stream of biological threats to health and safety. These threats range from pandemic flu and multiple-resistant pathogens like "MRSA" (*Staphylococcus aureus*) to food borne salmonella and *E. coli*. The diversity of sources, threats and consequences produce a very challenging environment for detection, diagnosis and alert. More significantly, failure to meet the detection and identification challenge results in a range of consequences, from massive food recalls and economic loss to morbidity and mortality. To meet this challenge, a wide variety of products have been introduced ranging from single threat diagnostics to prototype surveillance sensor systems. However, these responses to the market have limitations in stability and scalability and, in particular, their dependence on inherently unstable biological agents, like antibodies, places severe limits on both their economics and applications. Most importantly, these products are generally targeted to a single agent, which may not resemble the next threat. Clearly, what is needed is a sensor system that is stable and scalable to meet the demands of an impending pandemic and capable of spanning the range of specificity from a generic pathogenic virus alert to a multiplexed response and read-out for continuous surveillance. The combination of RECEPTORS' CARA platform and VeriChip's signal transduction and communication capabilities provides both the technology and the expertise required to build an integrated bio-threat sensor system.

STRATEGY

The spectrum of bio-agent defense ranges from sampling and capture to delivery of a diagnostic result via a sensor platform. The bio-agent spectrum includes a very diverse range of targets from protein toxins to pathogenic viruses and microbes. The strategic goal of this program is to build an integrated suite of sensor products focused on bio-agent surveillance, identification and alert. The product and market prototype system will focus on the development of a pandemic virus triage system (**Figure 1**) based on critical virus sensors, especially pandemic agents like H1N1 (SWINE FLU), H5N1 (BIRD FLU) and SARS. The triage system will provide multiple levels of identification; the first will identify the agent as virus or non-virus, the second level will classify the virus and alert the user to the presence of pandemic threat viruses, and the third level will identify the precise pathogen. Specific commercialization goals will include Point-of-Intercept to Point-of-Care, that is, from field to healthcare, sensors.

TECHNOLOGY

RECEPTORS' AFFINITY by DESIGN™ technology (US Patent 7,504,364 "Methods of Making Arrays and Artificial Receptors"; additional US and worldwide patents pending) is based on an efficient and scalable high-throughput approach to the discovery and application of stable and selective binding environments. Our SMART MATERIALS products and applications are built on our core competence of Surface Functionalization for Selective Binding (**Figure 2**). RECEPTORS' CARA™ discovery platform (**Figure 3**) is efficiently directed to the development of sensor products and applications (US Patent 7,469,076 "Sensors Employing Combinatorial Artificial Receptors"; additional US and worldwide patents pending), especially as applied to the closed-cycle sensing system with its critical combination of a target binding environment

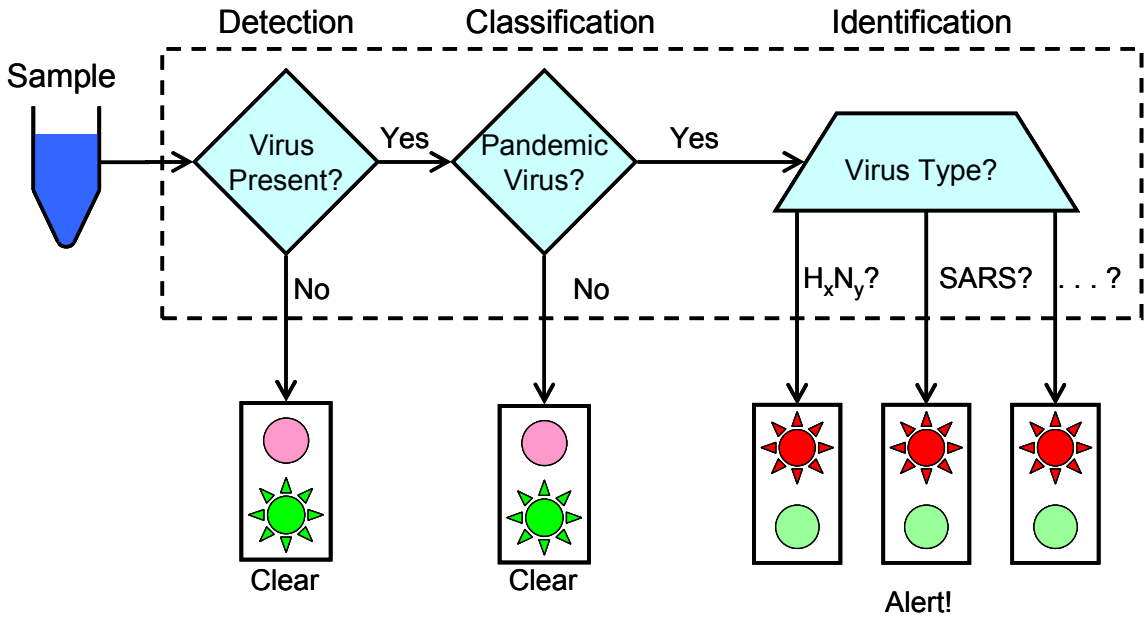


**Figure 1**. Schematic of the pandemic virus triage system. Three levels of threat identification are integrated into the diagnostic devide: confirmation of virus presence, classification of the virus as a pandemic-risk, identification of the specific virus.

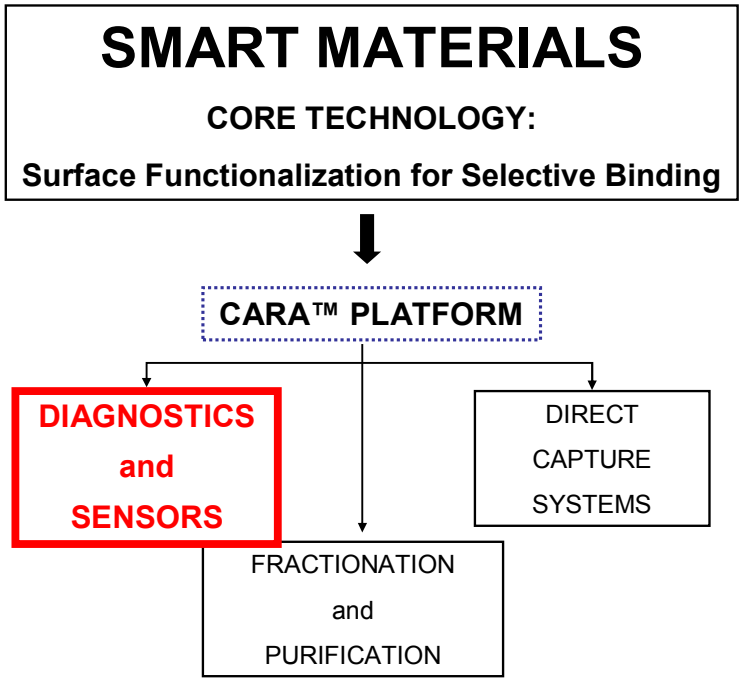


**Figure 2**. RECEPTORS core technology and application platforms.

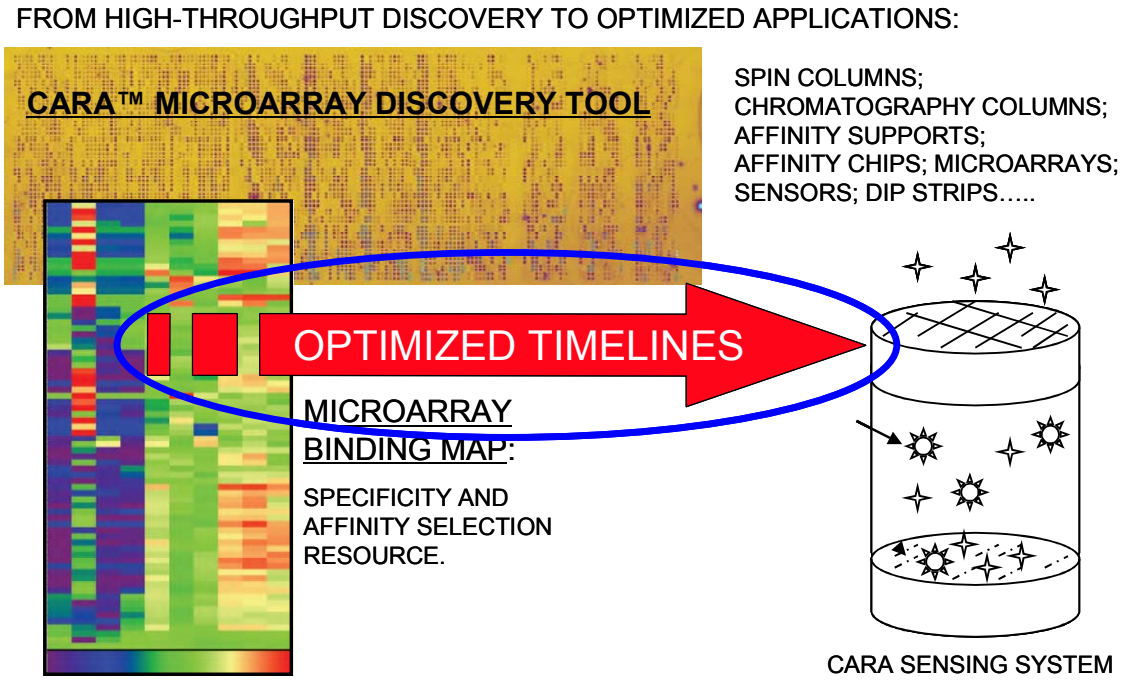


**Figure 3**. Schematic depicting RECEPTORS' binding environment selection and sensor development workflow. The high-throughput nature of binding environment selection and optimization to threat targets enables rapid development of products designed to address current and emerging pandemic threats.

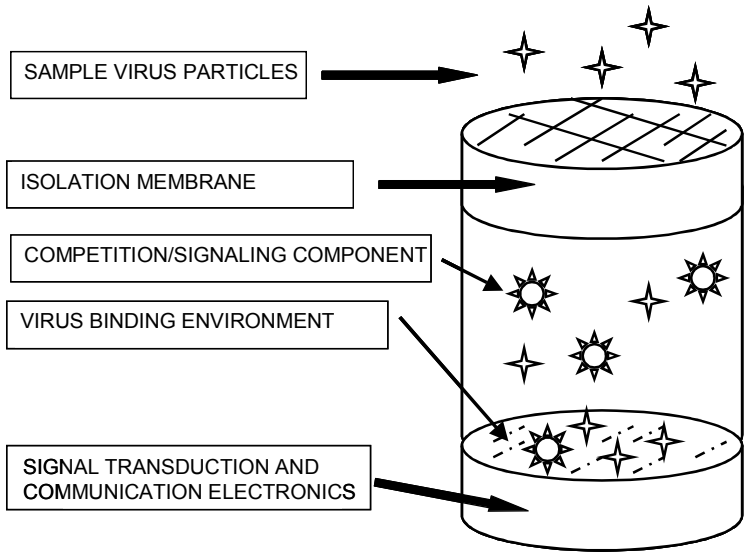


**Figure 4**. Closed-cycle sensing system. Critical components include the binding environments and the competitor agent.

with a competitor reagent. The sensing system, as illustrated in **Figure 4**, can be targeted to the products and applications required for bio-threat detection and diagnosis, ranging from Point-of-Intercept to Point-of-Care (**Figure 5**) surveillance and diagnostic sensor systems. The critical closed-cycle sensing system has been proof-of-concept demonstrated using a glucose sensing system model. (**Figure 6**). This model is being further developed into an integrated system for *in vivo* glucose monitoring (**Figure 7**) through incorporation of VeriChip's signal transduction and RFID communication technologies (US Patent 7,125,382; "Embedded Bio-Sensor System"). Our experience with the glucose sensing system program, in combination with our systems for the application of our CARA high-throughput screening platform, has established the development workflow that will be applied to this bio-threat development program.

PRODUCTS AND PROGRAM PLAN

This program will focus on the development of pandemic flu sensors that can be applied to both single-point (single target virus) and multiplexed (multiple target virus) sensor systems (as illustrated in **Figure 5**). Specific products include:

**PRODUCT:** "YES/NO", SINGLE-USE SENSORS that will screen for single or multiple target presence/absence.
**PRODUCT:** PANDEMIC SURVEILLANCE SENSOR SYSTEM that will provide multiplexed alert to a range of target agents.

PROGRAM PHASE I. TARGET VIRUS SENSING SYSTEM

There are several key components to these products, the most critical of which are the development of binding environment and competitor pairs for each virus target (as in FIGURE 4). The competitive interaction of the target virus, the binding environment and the competitor will produce a signal that is proportional to the presence of the virus. FIGURE 3 illustrates the general flow scheme that is utilized by RECEPTORS to build selective affinity environments for a wide variety of applications. The critical steps in the demonstration of the target sensing system are development of the target virus selective binding environment and the labeled competition and signaling component. The steps in this process, which will utilize RECEPTORS' established CARA™ workflow and sensing system competitor expertise, will be repeated for each target virus:
-- Combinatorial preparation and high-throughput screen selection of candidate competitor agents.
-- CARA™ microarray-based high-throughput screen selection of candidate binding environments.
-- Combination and optimization of binding environment and competition / signaling component to demonstrate proportional response to virus presence / absence.
-- Optimization of candidate binding environments for target sensitivity and specificity.

PROGRAM PHASE II. SENSING SYSTEM AND ELECTRONICS SIGNAL TRANSDUCTION INTERFACE. The sensing system developed in Phase I will provide a target virus signal via the competitive binding of the fluorescent or visibly labeled competitor agent versus the target virus to the virus selective binding environment. Signal transduction will be via optical to signal electronics with read-out and report. The

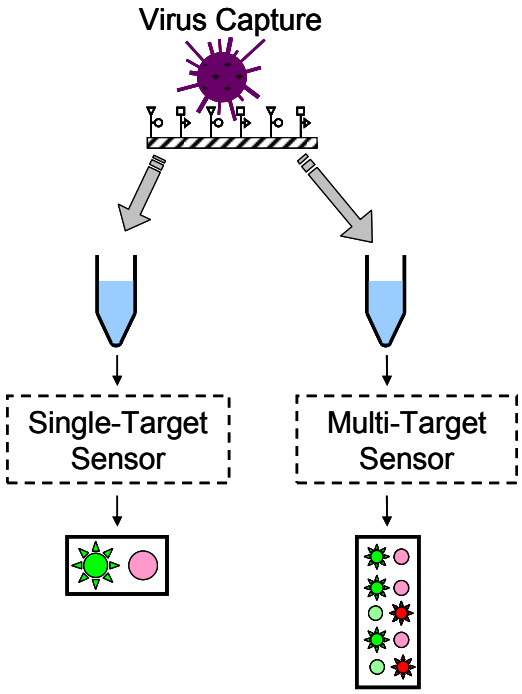


**Figure 5**. Schematic depicting biothreat detection diagnostic systems.

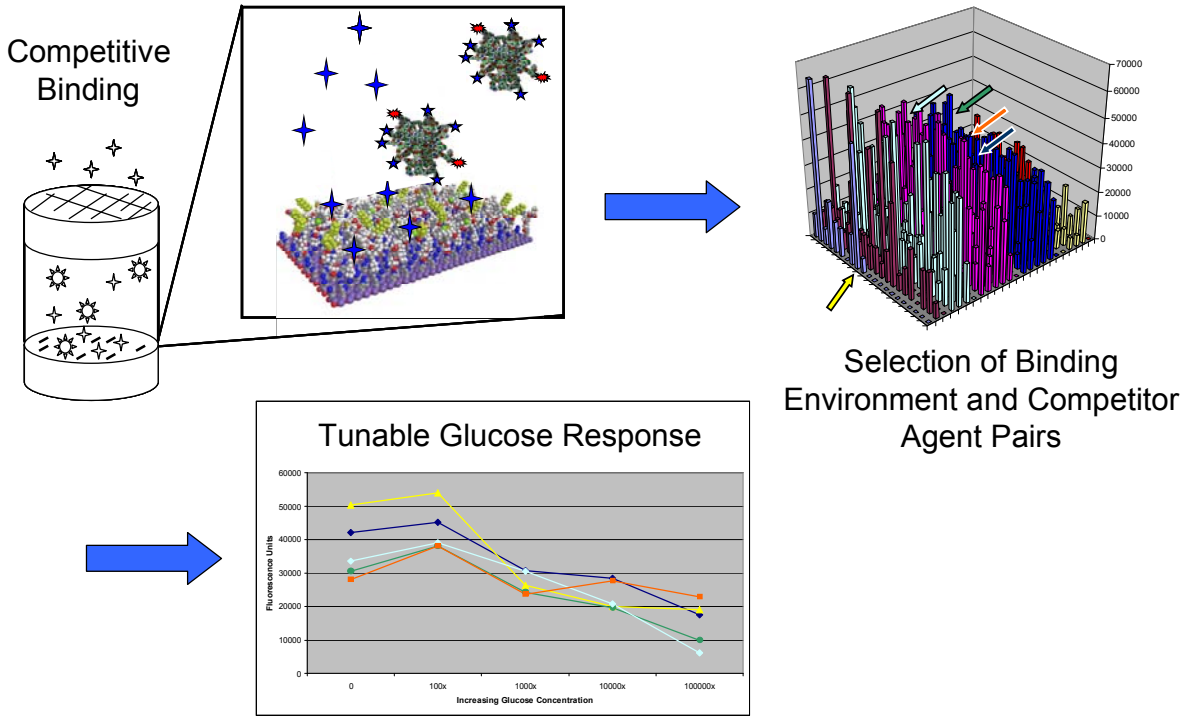


**Figure 6**. Glucose sensing system proof-of-concept. Selection and optimization of competitor agent – binding environment pairs enables control over the glucose response.

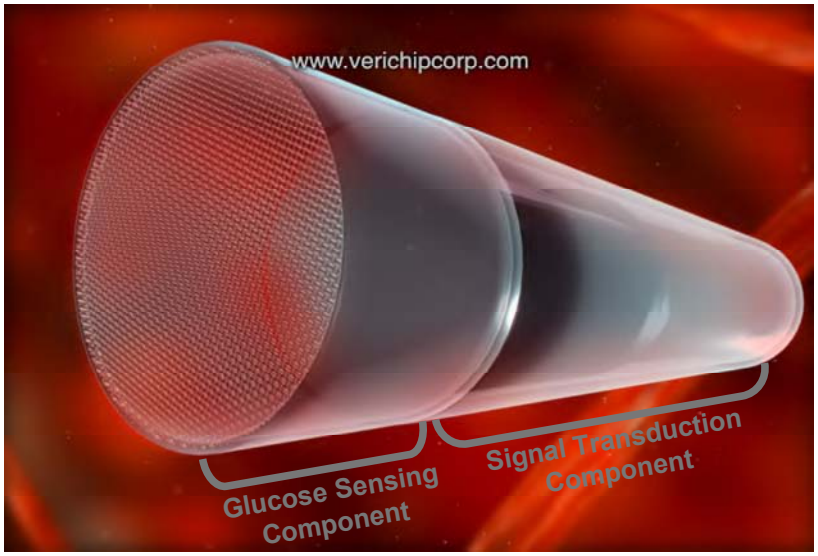


**Figure 7**. Illustration of an implantable glucose sensor which houses an integrated sensing system with signal transduction and RFID communication capability.

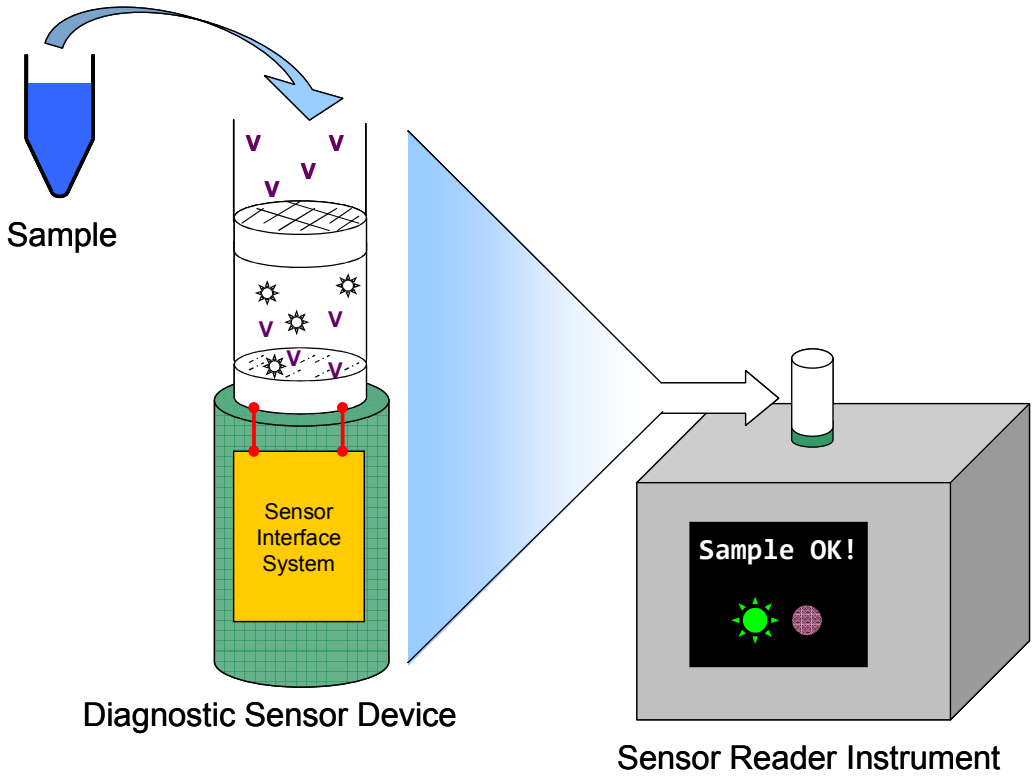


**Figure 8**. Diagram of the integrated virus sensor system which will include a single or multiplexed virus sensing system, optical signal transduction, and communication electronics.

electronics package will be contained in a base or hand-held instrument suitable for both field and point-of-care applications (as illustrated in **Figure 8**).

PROGRAM PHASE III. INTEGRATED SENSOR DEVELOPMENT. The prototype virus sensors will be produced by integration of either single or multiplexed sensing systems with optical signal transduction that is coupled to the application specific, sensor integrated circuitry and the communication electronics (for example, **Figure 8**).

SELECTED REFERENCES

Morse, et.al., "Next Flu Pandemic: What to do Until the Vaccine Arrives?", Science, vol. 314, p. 929 (2006).

**Criteria for Rapid Influenza Diagnostics**

P. Lu, "Early Diagnosis of Avian Influenza", Science, vol. 312, p.337 (2006).

WHO Recommendations on the use of Rapid Testing for Influenza Diagnosis, see www.who.int/csr/disease/avian_influenza

Rapid Diagnostic Testing for Influenza, see www.cdc.gov/flu.

**Synthetic Receptors**

Schader, T. and Hamilton, A.D. (Eds.) Functional Synthetic Receptors, Wiley-VCH Verlag GmbH & Co. KGaA (2005) 428pp.

**Sensors**

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