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BIOSENSORS ACTIVITIES AROUND THE GLOBE

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Since there are well over 500 companies and research organizations worldwide involved in biosensor development, it is important to note that the major biosensor players were identified in terms of the following criteria: publication output / quality, scientific impact, reputation, and size. The commercialization of biosensor technology has significantly lagged behind the research output. The rationale behind the slow and limited technology transfer could be attributed to cost considerations and some key technical barriers. Successful biosensors must be versatile to support interchangeable biorecognition elements and in addition miniaturization must be feasible to allow automation for parallel sensing with ease of operation at a competitive cost. A significant upfront investment in research and development is a prerequisite in the commercialization of biosensors. The progress in such endeavors is incremental with limited success, thus, the market entry for a new venture is very difficult unless a niche product can be developed with a considerable market volume.

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1. Introduction

Biosensors have captured the imagination of the world's scientific and commercial communities by combining interdisciplinary skills of biologists, physicists, chemists and engineers to provide innovative solutions to analytical problems. Biosensor technology is based on a specific biological recognition element in combination with a transducer for signal processing. Biosensors are detecting devices that rely on the specificity of cells and molecules to identify and measure substances at extremely low concentrations. Biosensors have been applied to a wide variety of analytical problems including in medicine, drug discovery, the environment, food, security and defense.

The potential growth in the world biosensor industry is remarkable; the emerging Biosensor market is expected to grow at over 9% in the coming years thus becoming one of the fastest growing sectors in the World. As stated by the recent report published by Global Industry Analysts Inc, United States and Europe dominate the global market for medical biosensors, collectively capturing 69.73% share estimated in 2008. The market in Asia-Pacific is projected to reach US$794 million by the year 2012. In medical diagnostics, the majority of biosensors (about 90%) are included in blood gas analyzers, electrolyte analyzers, glucose meters, and metabolite analyzers.

Over half of the biosensors produced worldwide are employed in glucose meters. With a diabetes epidemic underway, there exists strong growth opportunities for diabetes management tools, such as glucose meters. Over the years, glucose-monitoring meters have undergone a sea change, with recent entries featuring wireless and sensor technologies and noninvasive glucose monitors. Sales in United States, the largest market for Glucose biosensors are expected to reach US$1.28 billion by 2012. In Europe, Germany, United Kingdom and France, together, cover 55.3% of the biosensors market estimated in 2008. Bioluminescence-based biosensors gained immense popularity as a screening procedure for testing water quality in the key nations such as

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France, Germany, Spain and Sweden. Revenues in the German Environmental Biosensors market are projected to climb at the fastest rate to reach US$32.7 million by the year 2015.

Recent advancements in the field of bio electronics and biotechnology have provided systems that are able to efficiently transduce biological events using rapid, label-free electronic devices. This progress has led to the improvement of biological sensing platforms demonstrating the potential to be applied for the rapid screening of biological samples and point-of care applications. Particularly, the tailoring of new biomaterials by bio-genetic engineering allows to create new enzymes and protein receptors and to engineer monoclonal antibodies, aptamers or nucleic acids for non-biological substrates thus helping their integration in electronic devices. These electronic devices are mainly based on Carbon Nanotubes, Nanowires, Graphene sheets, Field Effect Transistors, piezoelectric crystals, scanning tunneling microscopy tips and others.

The biosensors industry comprises two types of participants including companies developing biosensor-based devices and developers of biosensor technology. Key players engaged in developing biosensor technology include Abbott Laboratories Cranfield Biotechnology Center, LifeSensors Inc., Biacore International AB, DiagnoSwiss, Panbio, Applied Biosystems and HTS biosystems. Leading manufacturers of biosensor-based devices include - Abbott Point Of Care Inc., Cranfield University, Lund University, New Mexico State University, University of Michigan, University of Florence, Coventry University, Potsdam University and BST Berlin, Ben-Gurion University of the Negev, University of Neuchatel/University of Geneva, and Roche Diagnostics Ltd.

This report aims to provide an overview of biosensor technology and biosensors-based devices focused on contributions related to innovative bioelectronics tools useful for clinical and biological applications, biodefense and food processing, bio (nano) sensors, cells and bio-receptor arrays, electronic bio-circuits for specific cell signaling, devices for proteins detection and study of their conformational structure.With some technical hurdles associated with the biosensor development. These hurdles include relatively high development costs for single analyte systems and limited shelf and operational lifetimes of biorecognition components.

2. Universities

2.1 Cranfield University

Medisense home blood glucose monitor which the worlds most successful biosensors to date has been developed by the Institute of Bioscience & Technology at Cranfield University [1] (http://www.cranfield.ac.uk/ibst/). They have created the first, fully integrated, blood sampling and glucose measurement device with collaboration of pelikan Technologies in Palo Alto (USA).This system have been provided with facility of painless for blood sampling and during glucose measurement. Cranfield University has developed a field based supercritical Fluid Extraction(SFE) device and protocol which is used in conjunction with a commercially available Rapid Assay Kit, where polycyclic aromatic hydrocarbon can be measured with detection levels of 0.5 to 100ppb present in the environment [2]. There is development of an electrochemical sensor for determining ultra-low concentrations of chlorine in fresh water where free total and combined chlorine can be detected up to 0.002ppm and can be used by unskilled persons. They have developed hand-held electrochemical-based biosensor for the detection of traces of pesticides. Some of other developments in biosensors at Cranfield University in Institute of Bioscience and Technology (IBST) are as follows: a) development of immunosensors, b) design and fabrication of diagnostic devices, c) biomimetic sensors, DNA chips & detection of infectious agents, the development of enzymes electrodes.

2.2 Lund University

They are focused on investigating heterogeneous and intraprotein Electron-Transfer of ligninoltic enzymes for the development of amperometric biosensors for the detection of hydro peroxides, carbohydrates, phenols and catecholamine's [3],(http://www.analykem.lu.se/).They have also undertaken extensive work on the development of biosensors for on-line analysis of fermentation processes where research focused on developing autoclavable microdialysis probes. They have developed another emerging area of bioelectrochemical research by the development of detection techniques based on spectroelectrochemical method. The development of biosensors for the determination of chemically modified starch and cellulose is another aspect of their development.

2.3 New Mexico State University

Their main focus area is on nanobioelectronics in which nanomaterials are used for analysis of biomolecules. There is development of use of carbon nanotubes (CNTs) for amplifying the recognition and transductions events of enzymes-based biosensors. Their other ground-breaking work shows that it is possible to develop a micro fabricated device, which integrates the multiple steps of electrochemical enzymes immunoassays on chip platform [4], [http://www.chemistre.nmsu.edu/research/sensors/srg/srg.html].

Beside this, they are engaged in the development of the following: a) implantable in vivo glucose biosensor, b) development of nucleic acid and protein biosensors, c) designing new detection schemes for microchip electrophoresis, d) the development of miniaturized analytical system, micro separation chips and micro fluidic devices, e) micro-fabricated enzyme electrodes f) nanoparticle-based bioassays, g) biorecognition-induced formation of nano-materials, h) remote sensors for environmental monitoring and security surveillance, i) developing techniques for ultra-trace measurements, j) designing nano-materials for electrical assays.

2.4 Tokyo University of Technology & University of Tokyo

They have contributed significant research work in the development of biosensors technology by developing the first microbial biosensor. There is development of a range of biosensors for biochemical oxygen demand (BOD), cyanide, detergents, dioxin, plankton, phosphate at Tokyo University of Technology & University of Tokyo [5]. The development of DNA array fabricated on glass substrate and surface Plasmon-resonance probe with an integrated reference sensor are some of their recent work.

Their current research activities primarily focus on the design & development of DNA and proteomic chips. The design & synthesis of bifunctional, environmental bioengineering and the design of bionics concepts are other aspects of their research activities.

2.5 University of Connecticut

There is the development of implantable sensors and biomaterials in the Health Centre & School of Medicine (University of Connecticut) [6], (http://www6.uchc.edu/biomaterials/home2.html. They have undertaken basic and applied research on tissues/ materials behavior and they have collaborative links with researches from the University of South Florida. Restoration, reconstruction biosensors and drug delivery system with in the clinical areas of orthopaedics, endocrinology, prosthodontics, restorative dentistry, oral surgery, surgery, orthodontics, endodontics and pharmacology are some of other clinical research activities. Recent work is the development of a miniature implantable biosensor with a telemetry electronics package for remote monitoring of glucose along with developing methods for improving the biocompatibility of sensors [7], [8].

2.6 University of Florence

University of Florence is responsible for some groundbreaking work on biosensors. (http://srv.chim.unifi.it/ana/). The following is a list of projects/activities undertaken at this university: a) electrochemical immunosensors for PCB detection; b) development of screen-printed electrodes,; c) developing biosensors for pesticide detection; d) biosensors for food analysis; e) bacterial contamination detection; f) development of biosensors for the detection of heavy metals; g) electrochemical immunoassays for algal toxins, PCB detection; h) development of electrochemical DNA sensors; i) development of optical sensors for the detection of potassium in whole blood j) development of piezoelectric biosensors; and. Some recent work at university of Florence is concerned with the development of a DNA-based surface Plasmon resonance (SPR) biosensor for the detection of TP53 mutation [9].

2.7 University of Michigan

University of Michigan is responsible for innovative work on improving the biocompatibility of implantable sensors and devices [10],(http://www.umich.edu/~michchem/faculty/meyerhoff/). They have tackled biocompatibility by exploiting the use of nitric oxide (NO) release polymers. These polymers slowly release NO as water is absorbed into the polymers (NO plays an important role in suppressing platelet adhesion and thrombus formation). An alternative approach is being developed that incorporates copper into the polymers.

It is believed that copper ions act as a catalyst for nitrosothiols, which are found in the bloodstream. The synthesis, characterization and biomedical application of materials that release/ generate nitric oxide (NO) is a major thrust of the work; however, other research activities involve designing novel electrochemical and optical chemical sensors based on thin polymeric films doped with selective host compounds, and the development of novel non-separation immunoassay methods.

2.8 University of Tuebingen

This University has a long history in developing optical-based immunoassay techniques for the detection of analytes in environmental samples [11]. Two systems are available, the River Analyser (RIANA) and the automated water analyser computer supported system (AWACSS), which are both based on a fluorescence optical system Total Internal Reflection Fluorescence (TIRF) and have been developed by this University. The sensor is commercially available as a demonstration prototype and may be adapted to measure any analytes that can cause the developement of an immunogenic response. It has been demonstrated in the field and was able to quantify multi-analyte concentrations in real samples with detection levels of below 0.1µg/l. The AWACSS analyses multiple analytes, one at a time in a quasi-continuous way with each measurement taking around fifteen minutes. The detection levels are similar to the RIANA system [12], [13].

2.9 Coventry University

In the Centre of Molecular & Bimolecular Electronics at (Coventry University) has been developed an optically-interrogated sensor system for the detection of nitrogen dioxide, in which a thin film of an active substrate is exposed to a gaseous ambient and optical changes recorded [14]. The prototype device responds in some seconds at room temperature and allows detection down to 100 ppb [15], [16].

2.10 Potsdam University and BST Berlin

They have developed a portable prototype device with an integrated amperometric biosensor that uses glucose dehydrogenase (GDH) modified thin-film electrodes to monitoring the phenolic content of water samples [17], [18].

2.11. Universidad de Alcalá de Henares

They have reported the production of screen-printed electrodes based on glassy carbon powder and containing tyrosinase and transduction chemistry [19]. These electrochemical strips, including a Ag/AgCl reference electrode and the counter electrode, are incorporated into an automatic FIA system (TRACE Analysensysteme GmbH) for continuous operation. The analytical performance of these sensors does not demand preconcentration steps and water samples can be injected directly into the automatic system. The obtained results are expressed as biosensor index and can be compared with the official method of phenol index [20].

2.12 University of Ulster

The University of Ulster has developed a biosensor for the determination of flavanols using either plant tissue material (polyphenoloxidases or commercial tyrosinase) immobilized in either a carbon paste electrode or screen-printed in with modified polypyrrole[21],[22]. The method relies on the electrochemical reduction of a quinone produced from the catalysed oxidation of the phenolic compound by ambient oxygen. It detect a broad range of analytes containing a catechol (1,2-dihydroxybenzene) group and this includes dopamine as well as a range of polyphenols of the catechin type found in flavanols. Detection levels are down to 2.5 μM [23], [24].

2.13 Perpignan University

BIOMEM Laboratory, University of Perpignan, focusing on the development of biosensors and MIPs in environmental and agro-food fields such as for the detection of microcystins in waters, monitoring of wine fermentation, analysis of pesticides in food and environmental samples [25].

2.14. University of Neuchatel/University of Geneva

Collaboration between these two universities has led to the development of four electrochemical-based devices able to detect metals in environmental samples. Three of their devices have been developed with a commercial partner, Idronaut SRL, for in-situ, on-line and field deployable modes, respectively [26]. One of the devices, the voltametric in-situ profiling system, is commercially available while the others remain at the demonstration prototype stage. Based on similar technology and methodology, devices differ by the use of different microelectrodes and electrode array configuration. Trace metal elements may be measured in fresh and salt water samples in aqueous samples at the sediment/water interface. They are also field-deployable. Detection is in the ppt-ppb range depending on the target element [27].

2.15. University of Ghent / Kelna, Belgium

They have developed RODTOX (Rapid Oxygen Demand and Toxicity Tester) 2000 is a respirometer type (BOD and Toxicity analyser).

The measurements are based on the on-line interpretation of the microbial respiration in an activated sludge-filled reactor. The BOD values obtained with the RODTOX 2000 correlate very closely with the BOD205 values ($r > 0.95$). Important application areas of the RODTOX 2000 are the municipal and industrial wastewater treatment plant. Here the RODTOX 2000 performs the on-line monitoring of load and toxicity of the influent and effluent water [28].

2.16. Bordeaux 3 University

The University has developed a sensor system that directly measures biodegradation rate in aquifers. The sensor can detect all degradable organics in groundwater. It detects the breakdown of hydrocarbons, but not selectively. The measurements are taken in situ as a continuous measurement. Detection levels are degradation rates of 1mg/l/day. The sensor system is currently in a prototype form and is being field-tested [30].

2.17. Ben-Gurion University of the Negev

The university has an optical fluorescence analyser that utilises genetically engineered luminescent bacteria for the detection of heavy metals (Hg, As, Cd, Pb and Zn); it can also detect genotoxicity levels. The device is fully portable and can be taken into the field. The device has been developed into a demonstration unit and can be used by an unskilled operator. Sample matrices range from soil sediment to any aqueous phase, with detection down to 2ppb [31].

2.18. University of Manchester Institute of Science and Technology UMIST RAD54-GFP

The UMIST RAD54-GFP test utilises yeast, a eukaryotic organism, as the biological component of the biosensor [32]. The biological core of the biosensor has already been developed beyond proof of principal, in the project "EMFID" – Environmental Monitoring by Fluorescence Induction and Detection. The existing biosensor is the product of a multidisciplinary collaboration between biologists and instrumentation scientists, fostered by the EC Environment and Climate Programme [33], [34].

2.19. University of Aberdeen / Remedios Ltd

The Universities, in conjunction with Remedios Ltd, a small technology transfer environmental biosensor consultancy, have developed a luminescence whole cell Toxicity sensor. The biosensor is currently being used by Remedios Ltd in its consultancy work for commercial clients. The biosensor requires a skilled technician and it is available commercially via consultation. Target analytes are all acutely toxic chemicals and metals and organics in the bio-available fraction (aqueous samples). The sensor will only provide a primary screen [35].

2.20. University of Nantes

The university has developed a bioassay based on a 96-well plate prototype immunoassay kit and an optical based biosensor that allows the detection of organo-tin compounds. These compounds such as tributyltin (TBT) and dibutyltin (DBT) are highly toxic biocides. Measurements are made in aqueous samples and have detection limits for the plate-based assay of 0.08μM and 0.0001μM (sub-ppb range) for TBT and DBT, respectively [36].

3. Companies

3.1 Abbott Laboratories

Abbott Laboratories is concerned with the diagnosis and treatment of diseases / illnesses [37]. In 1996, it acquired MediSense for $867 million, which was one of the first companies to commercialise the glucose biosensor technology. Abbott also broadened its product offering with the acquisition of International Murex Technologies Corporation in 1998, a firm concerned with microtiter-based immunoassays and microbiology products. In 1998, it launched two clinical chemistry analyzer systems, Alcyon and Aero set, along with Determine, a line of self- performing assays targeted for the health care markets. In 2001, it acquired Vysis, Inc., a genomic disease management company that develops and markets clinical laboratory products for the evaluation and management of cancer, prenatal disorders and other genetic diseases In 2001, the company launched the Precision Xtra, the first personal blood glucose monitor with ketone testing capability, and also received FDA marketing clearance for Sof-Tact, a fully automated blood glucose monitor to offer lancing, blood collection and glucose testing with a single press of a button.. Abbott has cemented itself in the top three largest biosensor companies worldwide after the purchase of Therasense for $1.2 billion and i-STAT for $392 million in early 2004. Abbott D contained in a test cartridge for single-use disposable blood testing. AbbottDiagnostics(http://www.abbottdiagnostics.com/) is a part of Abbott Laboratories, which provides a wide array of in vitro diagnostic instrument systems and tests for hospitals, reference labs, blood banks, physician offices and clinics. In 2009, Abbot's Ibis T5000 Biosensor system, designed to detect and characterize a broad range of infectious agents.(www.abbott.com/news-media/press-releases/2011-oct17.htm-50k-2011-10-17). Blood from a patient sample and several camel tissue specimens were analyzed using the Ibis T5000 biosensor (www.abbott.com/news-media/press-releases/2011Feb07_2.htm-50k-2011-11-19). Biosensor technology helped detect the earliest cases of the 2009HINI flu virus, and was recognized with top innovation awards (www.abbott.com/../annual_report/2009/download/Full_report.pdf-2010-03-09). Abbott has developed Biosensors System has the potential to identify virtually all bacteria, viruses and fungi without requiring users to predict the testing. (www.abbott.com/../annual_report/2009/operting_review.html-28k-2011-09-29). Abbott PLEX-ID biosensor was named the overall Gold winner of the 2009 awards. (www.abbott.com/news-media/rankings/detail.htm-62k-2012-03-21).

3.2 ABTECH Scientific Inc.

ABTECH is engaged in several strategic research partnerships with various Universities & Organizations (Virginia Commonwealth University, University of South Carolina, University of Pennsylvania, Pennsylvania State University, University of the West Indies, and Medical College of Virginia). ABTECH Scientific, Inc. is a biomedical diagnostics company founded in 1995(http://www.abtechsci.com/) that specializes in biosensor devices, biosensor instruments/ systems for the biomedical research community and for point-of-concern biomedical diagnostic applications [38]. ABTECH's has developed biochip technology, which is based on impedimetric detection of chemically amplified biochemical signals. The following proprietary products are marketed by the company: BioSenSysTM (performs biosensor-based immunodiagnostic assays for the monitoring of blood metabolites, therapeutic drugs, and microbiological agents); ToxSenTM (based on a multi-element array of differentiated whole cells it performs on- site chemical toxicity screening of water, wastewater and other effluent streams); EnVOCSysTM (a device for monitoring volatile / gas phase organic constituents in the expired breath at the sub-ppm level); beChipTM (a 64-element impedimetric array for bioelectronic detection of DNA hybridization).Recently they are engaging in development of (1) Implantable Biochip to Influence Patient Outcomes Following Trauma-induced Hemorrhag [39], (2) Development of an Implantable biosensor system for physiological status monitoring during long duration space flights [40], (3) Bioactive Electro conductive Hydro gels Yield Novel Biotransducers for Glucose [41].

3.3 Affymetrix

Affymetrix (http://www.affymetrix.com/index.affx), founded in 1991 as a division of Affymax N.V., began operating independently in 1992 [42]. The Company is a leader in the field of gene chip development for the detection of genetic diseases.Affymetrix's technology works well in identifying which genes correlate to a specific disease.

The Gene Chip microarray consists of small DNA fragments, chemically synthesised at specific locations on a coated quartz surface. The precise location where each probe is synthesized is known as a feature, and millions of features are contained on each array. Nucleic acids extracted and labeled from samples are then hybridized to the array, and the amount of label can be monitored at each feature, resulting in a wide range of possible applications on a whole- genome scale, including gene- and exon-level expression analysis, novel transcript discovery, genotyping, and re-sequencing .(http:www.affymetrix.com).

3.4 Bayer AG

Bayer AG (http://www.bayerdiag.com) is a company that deals with the health care and medical products industry [43]. The company offers a variety of Glucometer instruments for blood glucose testing and in vitro diagnostic immunoassay system for hepatitis A virus. The company has received several granted patents, notably US patent 6,531,040 that describes an electrochemical sensor for detecting analyte concentration in blood (http://www.bayerdiag.com). The glucometer Elite Diabetes Care System is a blood glucose monitoring system based on an electrode sensor technology. Capillary action at the end of the test strip draws a small amount of blood into the detection chamber and the result is displayed in 30 s.

3.5 Biacore International AB

Biacore (http://www.biacore.com/lifesciences/index.html) develops, manufactures and supplies analytical systems for antibody characterization, immunogenicity, biotherapeutic development / production, and proteomics [44]. Biacore is a global market leader in affinity-based biosensor technology. Target groups consist primarily of medical and life science research laboratories. However, expansion is also being pursued in other areas, such as food analysis. Biacore had sales of SEK 288.8 million in 1998 and an operating income of SEK 52.8 million. Based in Uppsala, Sweden, the company is listed on the OM Stockholm Exchange and NASDAQ in the U.S. (www.biacore.com).

Development of the first commercial product began in 1989, which produced BIAcore®, the world's first SPR-based analytical instrument for studying biomolecular interactions. Based on SPR, Biacore's technology provides a non-invasive, label free system for studying bimolecular interactions. There are over 2800 references citing Biacore across therapeutic areas including cancer, neuroscience, immunology and infectious diseases biosensors can monitor up to 100 biological evaluations/day. The SPR array chip technology is expected to process 100,000 biological evaluations/day. Despite its versatility, SPR system becomes less applicable for detecting biomolecules which have a molecular weight of less than 5000Da. However, a surface-competition assay format was developed that allowed indirect detection of small-molecule binding [45]. Other improvement in SPR instrumentation has enabled detection of small molecules such as drugs. [46].

3.6 Cygnus, Inc.

It (http://www.cygn.com/homepage.html) was founded in 1985 Its focus on development, manufacture and commercialization of glucose monitoring devices [47].The Cygnus,Inc developed noninvasive and continuous monitoring technologies and FDA has approved so far as an automatic and noninvasive frequent-sampling glucose monitor___the GlucoWatch Biographer. This instrument received agency approval in March 2001 as an adjunctive device to supplement, not replace, blood glucose measurements. The second-generation GlucoWatch G2 Biographer was approved in March 2002and again in August 2002 for pediatric use.

The Cygnus' GlucoWatch® Biographer provides automatic and non-invasive measurement of glucose levels from fluid between the skin tissue rather than blood. However, the company has an arbitration matter with Ortho-McNeil Pharmaceutical, Inc., a Johnson & Johnson company, and is winded all activities in 2003 followed by the scale of its glucose-monitoring assets to Animas Corporation and Animas Technologies LLC in 2005. However, Animas was no longer selling the current model GlucoWatch G2 Biographer system, effective July 31, 2007. The company will continue to sell AutoSensors and provide customer support for the GlucoWatch system through July 31, 2008 (http://www.glucowatch.com).

3.7 DiagnoSwiss

DiagnoSwiss S.A. is a privately held biotechnology company created in summer 1999 and specialized in the development and commercialization of advanced biochip technologies [48].

It designs polymer micro-systems for high performance protein analysis, drug discovery and industrial control. Relying on its proprietary technologies, DiagnoSwiss provides disposable micro-chips with integrated micro-electrodes that enable fast analysis, low sample and reagent volumes, high throughput, reduced analysis costs, easy data processing and improved efficiency. With particular skills in micro- fabrication, micro- fluidics, electrochemistry and immunology, its main product lines are:

Polymer Micro-chips: DiagnoSwiss markets highly cost effective disposable micro-chips with integrated gold electrodes. Mass production of electrochemical micro-chips is made by plasma etching of polymers like polyimide, and comprise fluid handling and electrochemical detection means (production capacity >100'000 pieces/day). Micro-channel networks (typical volumes of 50-100 nL) provide micro fluidic tools with large surface/volume ratio and good immobilization properties that are specially designed for fast and parallel analysis.

Disposable affinity tests: Its micro-chips have been developed for high performance immunological assays in low volumes. The strength of our micro-systems is to drastically accelerate the response time (typically <5 min instead of 2-3 hours for a quantitative assay), while maintaining performances as high as those required in medical diagnostics (pM detection limit for a dynamic range of 5-6 orders of magnitudes). These advantages afford assay standardization, low reagent consumption and multi-analyte testing, in customized platforms.

DiagnoSwiss' electrochemical biosensor chips find their main applications in protein affinity tests (medical diagnostics, microbiology, food, warfare's, pharmaceutical research, proteomics, industrial control) and DNA analysis (genomics, medical diagnostics), that can be carried with simplified infrastructure and outstanding efficiency.

Biosensor-Chip is the core element of diagnoSwiss technology. This consumable chip, which emanated from the combination of micro-fluidics and electrochemistry technologies, is a revolutionary device which is easily amenable to a wide range of analytical application

DiagnoSwiss chips are factually polymer cartridges with an array of micro-cells designed for running magnetic bead-based ELISA protocols with standard immunology reagents.

ImmuSpeed™ is an automated micro- fluidics-based platform, designed for running bead-based ELISA tests with standard immunology reagents by DiagnoSwiss.

3.8 Lifescan

LifeScan (http://www.lifescan.com) is primarily concerned with the commercialization and development of the glucose biosensor for diabetes management [49]. The firm is part of the Johnson & Johnson family of companies. LifeScan presently markets an array of products for blood glucose testing. In 2001, it introduced the OneTouch® Ultra® blood glucose monitoring system, which is a painless stress-free measuring device. The InDuo® system, which is one of the world's first blood glucose- monitoring and insulin-dosing system, was unveiled in 2001. This device features a 5-second test time, wide temperature range, arm-testing capability, memory to indicate time since last dose, 6-second insulin delivery countdown, and an adjustable dosing mechanism. In 2003, LifeScan launched the OneTouch® UltraSmart® blood glucose monitoring system. This system features a 3,000-record memory, SmartButtons™ to enter health, exercise, medication and meal information, a FastFacts™ Button to review results and graphs.lifeScan has an exclusive U.S. agreement with Medtronic to develop a new blood glucose meter that will wirelessly transmit glucose values to Medtronic's smart MiniMed paradigm insulin pumps and Guardian REAL-Time continuous monitoring systems.

Universal Biosensors, Inc. (ASX: UBI) today announced that Life Scan, Inc. has launched the One Touch® VerioTMIQ system in the United States. LifeScan's press release in relation to the product is attached.

The launch represents a major milestone in the global roll-out of the OneTouch® VerioTM technology. The OneTouch Verio system is now available in all major self monitoring blood glucose (SMBG) markets including the United States, Canada, Europe and Australia. The continuing global roll-out further demonstrates LifeScan's commitment to the OneTouch Verio technology.

The SMBG market in the US in 2010 was approximately US$3.84bn which represents approximately 40% of the global market. The US SMBG market is expected to grow to US$5.59bn by 2015.

Life Scan is the market leader in North America with approximately 33% of the SMBG market in 2008.

3.9 Neogen Corporation

Founded in 1982, Neogen Corporation (NASDAQ: NEOG) has grown to more than 600 employees in multiple U.S. and international locations, and a worldwide presence. Neogen develops, manufactures and markets a diverse line of products dedicated to food and animal safety [50].

In recognition of this success, Neogen has been repeatedly named to Forbes Magazine's list of the Best Small Companies in America and was chosen by the NASDAQ National Market to be included in its top tier of listed companies, the Global Select Market.

The company markets the GeneQuence Automated System, which is a fully automated 4-plate processing system for the detection of pathogens in raw ingredients, finished food products, and environmental samples. The AccuPoint ATP Sanitation Monitoring System, which provides sanitation monitoring capability in a handheld unit.

The Company's Lansing, Mich.-based Food Safety Division develops and markets dehydrated culture media, and rapid diagnostic test kits to detect food borne bacteria, spoilage organisms, mycotoxins, food allergens, genetic modifications, drug residues, plant diseases, and sanitation concerns. Neogen's Lexington, Ky.-based Animal Safety Division develops and markets a complete line of diagnostics, veterinary instruments, veterinary pharmaceuticals, nutritional supplements, disinfectants, and rodenticides. Neogen's GeneSeek subsidiary based in Lincoln, Neb., is the leading global provider of DNA testing for animal agribusiness and veterinary medicine.

The company also supplies ELISA test kits/reagents and testing equipment for food borne bacteria, drug residues, toxins, and biologically active substances. Recently (March 14, 2008),

Neogen has received approval for the new United States version of its quick and easy BetaStar® test for dairy antibiotics in milk. TheBetaStar® US test (AOAC-RI No. 030802) is an extremely simple dipstick test that detects dairy antibiotics in the beta-lactam group, requiring only minimal training and equipment to produce consistently accurate results.

3.10 Panbio

Panbio was established in 1988 and listed on the Australian Stock Exchange in 2001 (ASX: PBO) [51].

Panbio manufactures and markets innovative tests to aid in the diagnosis of infectious disease and is recognized as a world leader in tests used in the diagnosis of flavivirus and other arthropod-borne viruses. Panbio also manufactures and sells a range of products for the diagnosis of diseases such as the Epstein-Barr virus, brucellosis, Q-fever and human herpes virus 6 (HHV-6).

Panbio has a history of market leadership in response to diseases that afflict millions of people and was 'first to market' with diagnostics for dengue fever, Ross River fever and West Nile encephalitis.

With a product portfolio covering over 30 infectious diseases, Panbio supports pathology laboratories and physicians in Australia, Asia, the Americas, Europe, the Middle East and Africa.

In research, Panbio is pursuing a major development in the platform technology underpinning in vitro diagnostic assays. This development is of a technology based on the concept of a homogeneous assay system, where a patient's sample is tested in a single test solution eliminating the multiple steps required in conventional enzyme immunoassay systems such as ELISA.

Recently, Panbio received US FDA clearance for its second generation West Nile virus test and has signed research agreements to develop improved diagnostics for Japanese encephalitis, leptospirosis and malaria. The company has patented the Oligo Rapid System, which is aimed at the 'Point of Care' market. (http://www.panbio.com.au.)

The Oligo technology provides the capability for multiplexing assays. Research activities are mainly directed towards the development of two platform technologies: a) Oligo Rapid Immunochromatography for point of care and b) Homogeneous Assay systems based on Enzyme Fragment Complementation (EFC) technology.

3.11. Pelikan Technologies, Inc.

The Pelikan Technologies Inc. (http://www.pelikantechnologies.com) is concerned to the development of hand-held diagnostic and monitoring devices for the testing and management of a variety of medical conditions [52]. Pelikan Technologies founded in 2001 and is concerned with development of hand-held diagnostic/ monitoring devices based on the seamless sampling technology. Pelikan unveiled its Pelikan Sun lancing device at the 63rd American Diabetes Association Scientific Sessions in June 2003. This lancing device is the first fully automated and self- contained system that allows a patient to execute the entire lancing process at the touch of a button in a virtually painless operation. Pelikan Technologies have developed a novel blood sampling / measurement technique with state-of-the-art miniaturisation and automation to develop a hand-held diagnostic monitoring device.

3.12 Roche Diagnostics AG

Roche Diagnostics (http://www.roche-diagnostics.com/) offers a range of biosensor products (Health & Life Sciences) for people working in medical laboratories, physicians' offices, pharmacies, life science research, and the diagnostic industry [53]. As for patent applications submitted by Roche Diagnostics, the majority of them have been issued for biosensors used for analyzing blood samples. In April 2003, Roche was issued a US Patent Number 6541216, entitled "Amperometric biosensor test strip". This invention allows the measurement of blood ketone levels.

Roche Diagnostics is a division of F. Hoffmann-La Roche Ltd (Basel, Switzerland) and conducts research mainly into biosensors that permit near-painless, continuous measurement of blood glucose level. It markets the Accu-Chek family of products / services for blood glucose monitoring.

Beside the development of biosensors Roche Diagnostics AG. Provides the devices as follows: LightCycler® Instrument for real time PCR; Rapid Translation System for protein expression; and the MagNA Pure LC Instrument for nucleic acid purification. It also provides kits and reagents for genomics and proteomics research, bioreagents for industrial use, products for food safety and pharmaceutical testing.

3.13 Applied Biophysics

Applied Biophysics, Inc developed ECIS® (Electric Cell-substrate Impedance Sensing) is a real-time, label-free, impedance-based method to study the activities of cells grown in tissue culture. These include morphological changes, cell locomotion, and other behaviors directed by the cell's cytoskeleton. This impedance-based cell monitoring technology was invented by Drs. Ivar Giaever and Charles R. Keese who founded Applied Biophysics, Inc [54].

The ECIS® approach has been applied to numerous investigations including measurements of the invasive nature of cancer cells, the barrier function of endothelial cells, in vitro toxicity testing as an alternative to animal testing, and signal transduction involving GPCR's for modern drug discovery.

Applied Biophysics (ABP) automates tissue culture research by measuring the impedance of mammalian cells cultured on small electrodes. This company has electric cell-substrate impedance sensing (ECIS) instruments, disposable culture ware and optional accessories designed to work with ECIS instruments.

Ivar Giaever (Nobel Prize in Physics 1973) and Charles Keese started ABP in 1991 to commercialize the invention they discovered while working for General Electric. Since the formation of the company the ECIS approach has been applied to numerous applications and there are now ECIS instruments in research labs, hospitals and pharmaceutical companies across the world.

3.14 The Spreeta and other SPR Biosensors

Spreeta is an electro-optical device utilizing surface Plasmon resonance to detect small changes in refractive index of liquids. The Spreeta device was developed by Texas Instruments, Inc. in the 1990s [55]. Device design incorporates a light-emitting diode (LED) illuminating a thin metal film (usually gold) in the Kretchmann geometry (needed to excite surface Plasmon's). The reflected light is detected by a photodiode linear array (which translates angle of reflection to pixel position) and the resonance (a dip in the reflectivity at a specific angle of incidence) denotes the refractive index on the outer surface of the metal film. Applications include real-time measurement of binding of antigens to antibodies attached to the sensor surface, monitoring changes in oil quality, and measuring sugar content in drinks (Brix level).

However, the Spreeta technology might not be as sensitive as the standard ELISA procedure (spangler et al., 2001). In 2008, the manufacturer of SensiQ (ICx Nomadics Bioinstrumentation Group, Oklahoma City, OK) just launched SensiQ Pioneer, a fully automated SPR platform while maintaining the cost affordability (http://www.discoversensiq.com). XanTec Bioanalytics GmbH of Germanyis another company that commercializes SPR biosensors (http://www.xantec.com).

3.15. Applied Biosystems and HTS biosystems

Applied Biosystems® instruments have been trusted in the lab for over 50 years by the world's top scientists has develop the 8500 Affinity Chip Analyzer and this technology is based on grating-coupled SPR and employs a single large flow cell so that 400 ligands can be spotted and analyzed at one time. This system is particularly well suited to examine antibody–antigen interactions and it can detect analytes with molecular masses down to 5000 Da (Applied Biosystems Application Notes about antibody characterization at [56]. For antibody, peptide, and DNA, the preparation of pertinent chips is relatively straightforward because these ligands retain their native structure throughout the preparation process involving drying and reconstitution steps. Patterning methods for more labile enzymes and receptors are still a formidable task and require more elaborate procedures. Nevertheless, the 8500 Affinity Chip Analyzer is expected to open up new possibilities for biosensor analysis. In parallel processing, the delivery of separate samples to the detector in a rapid manner and at constant concentration is not an easy task. Although several micro fluidics platforms have been developed to solve this problem, the SRU Biosystems [57] uses special 96- or 384-well plates with a colorimetric resonant grating on the bottom. The system employs a guided mode resonant filter to monitor refractive index changes at the sensor surface. This label free system is designed for end-point measurements to tracks analyte binding in each well and the entire plate can be read within fifteen s. This standard micro titer plate format can be easily integrated with other robotic systems for sampling and data output.

4. Conclusions

The development of ideal biosensors which are fast, easy to use, specific, and inexpensive, doubtlessly, requires the significant upfront investment to support R&D efforts and this is a key challenge in the commercialization of biosensors. To date progress in biosensor development is somewhat incremental with low success rates and there is the absence for huge volume markets except for glucose sensors. The future trend includes the integration of biosensor technology with leading-edge integrated circuit, wireless technology and miniaturization. However, one must carefully look at the special demands of analytical chemistry and technology feasibility prior to any decision making or commitment to undertake a new research project or development. From a technical viewpoint, a dream biosensor might be a combination of SPR with electrochemical detection to process "real-world" samples such as blood serum, environmental samples and other colored samples

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