Executive summary

Biomarkers Discovering

Biomarkers, or biological markers, are biochemical features that either directly or indirectly provide information about the presence of a disease and its progression (or remission) and effects of a drug compound on the disease. A biomarker has been defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, pharmacological responses to a therapeutic intervention". In addition to early diagnosis and health monitoring uses, b*iomarkers can reduce the costs and time required to get a drug from discovery to market.*

PrediGuard Mission Statement

Prediguard's aim is to develop the design of prognosis and diagnostic kits through the identification of relevant markers for a wide range of diseases as well as « ready to use » databases dedicated to drug discovery. To achieve its goal, PrediGuard has spent several years to develop innovative tools and has initiated a specific strategy enabling to generate valuable patents. Due to its specificities, it is expecting that PrediGuard will be a leading company in the field of personalized medicine testing within 5 years.

Both, sets of biomarkers and data bases will be marketed, as products, to companies involved in the drug discovery and diagnostic market. PrediGuard will provide licenses of newly discovered biomarkers to generate profits and visibility in the market place.

Contact: **Dr. Philippe Benech**

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Team Management

Dr. Philippe Benech, Ph.D.– CSO and founder

Research Director at the French Centre National for Research Scientific and at the National Institute for Health and Medical Research INSERM.

As senior scientist at the Weizmann Institute, Harvard Medical School and Curie Institute, he worked for many years on gene expression regulation at both, transcriptional and RNA processing levels. Identifying the genes involved in the antiviral state induced by interferon, he was considered as a pioneer in the discovery of cytokine signaling pathways. These discoveries led to a better understanding of the immune system and inflammatory processes.

He is the recipient of several grants and awards (laureate of the International Union Against Cancer, European Molecular Biology Organization, Medical Research Foundation, Association for Cancer Research, National League Against Cancer, AVENTIS Foundation for Medical Research). He was appointed from 1994 to 1998 as scientific advisor by the French Ministry of Research.

Founder of GeneSodi, he developed with his team, Predict Search™ a text mining based software, dedicated to the interpretation of data generated by gene quantification technologies such as microarrays.

Dr. Phlippe Halfon – Ph.D., M.D., Pharm.D.

Founder of several biotechnology companies focusing on antiviral drug discovery and development, including ACTgene, Alphabio, Genoscience Pharma. CEO of Alphabio Laboratory (Marseilles, France) in charge of the R&D. Nominated as one of the 30 best managers in France with Alphabio Laboratory.

Specialized in molecular virology and infectious disease. Worldwide virological expert for HIV, HPV and Hepatitis. Known for his innovative and pioneering work on HIV and HCV drug resistance and non invasive markers of liver fibrosis.

Member on scientist societies and European Expert for Institutional agency (ANRS, HAS). Received award of Tremplin –Entreprises in the Sénat-France

Consultant for Roche Diagnostics, France (1997-2000), and for Schering Plough, France (1998–2005).

Prof. Patrice Cacoub – Ph.D., M.D.,

Professor at the department of Internal Medicine at Pitié-Salpétrière Hospital (Paris). .

Adviser for several Clinical Research Agencies (ANRS, HAS). Nominated at the board of the Scientific Committee for Atherothrombosis

Reviewer for national and international medical revues.

Scientific Board

President: Prof. Miroslav Radman. Head of the INSERM unit1001 “Laboratoire de Génétique Moléculaire Evolutive et Médicale”(Necker hospital). Professor Radman is a nominated member of the Académie des Sciences. Recipient of numerous awards, including « le Grand Prix INSERM 2003. He is the founder of the Mediterranean Institute for Life Sciences.

Miroslev Radman is worldwide known for his work on the DNA repair mechanism that led to new discoveries in the aging process.

Team Structure

PrediGuard SAS: 1 CSO
1 Business developer
3 biologists
3 computational engineers

PrediGuard Historic Features

PrediGuard 's technology relies on innovative computational tools that were developed since 2002 by Dr. Philippe Benech and his team.

The decision to transfer this technology into PrediGuard was motivated by the need to target the US market in order to expand its activity.

PrediGuard. was incorporated in March, 2008. Its headquarters and laboratory facilities are located in Marseilles (France).

PrediGuard Technology

Identification of biomarkers requires the collection of huge amount of curated medical and scientific data that are already available (outsourcing) or generated through the use of an accurate high throughput screening technology (in sourcing).

PrediGuard has a recognized expertise in the interpretation of Gene Expression Profiles using Whole Genome Microarrays. This technology allows to analyze gene expression through the quantification of gene products (RNA) that are translated into proteins. Thus, it is possible to detect very slight modifications at a cellular level in response to any kind of stimuli, disease or therapy.

Since such a technology generates thousands of data at once, relevant information has to be captured.

P*rediGuard is currently gathering and combining data integrated within functional networks using its software PredictSearch®: a data mining-based tool that operates as a Scientific « Google » search engine to correlate markers with biological and physiological processes.*

PrediGuard has developed Gene Tracker®, a software that allows, starting from a given set of markers, to identify experimental conditions or pathologies where such set is found in an already built database containing more than 20,000 curated and normalized gene expression profiles.

Therefore, the way to collect data should lead to markers of functional significance enabling to diagnose very early events before symptoms to occur.

Business Model

PrediGuard's business model relies on the ability to: (1) perform **fee-for-services** in order to complete and promote our expertise in various fields of biology, (2) establish partnerships with known clinical investigation centres, (3) generate gene expression assessment for thousands of individuals years after years through the **BioPass®** service, (4) set up a highly valuable database, (5) discover reliable **biomarkers** from the collected data, and license these biomarkers at a substantial profit.
PrediGuard's business model may be compared to a four-stage rocket, stages 1-4 providing more and more quantitative and qualitative organized data in order to give more chance to the last stage (stage 5) to reach the orbit.

Fee-for-Services

Since 2003, our professional service (***http://www.prediguard.com***) has provided hundreds of studies enlightening specific compound activities to promote innovation, patent applications and marketing issues for our clients. These studies were performed on biological samples issued from on a wide variety of cells or tissues and covered different fields (virology, oncology, immunology, and aging). Customers are pharmaceutical/biotech companies such as Johnson & Johnson (US), Sanofi (France), Servier (France), Negma (France), Wockhart (India), InnatePharma (France), NTM (Russia), SECIA (UK) or cosmetic related companies such as Sederma-CRODA group (UK), LS-COGNIS groupe (Germany), SILAB (France), Estee Lauder (US), Bioderma (France), Secma BioTechnology Marine (France) and GIREX (France).

In addition to provide clues concerning the identification of activities or the mechanism of action of drugs or compounds, PrediGuard is more and more involved in clinical trials to define the molecular basis of the response to therapies.

In parallel with these professional services, PrediGuard has established and will still maintain academic collaborations in order to pursue collecting data on focused field of research and pathologies.

BioPass®

BioPass®, a personalized gene expression profiling-based consumer care assessment, is a breakthrough technology for defining and achieving personal medical follow-up ***(http://www.biopassprofiler.com)***.

BioPass® looks at the equilibrium profile and helps to monitor and maintain this equilibrium during the life span. It can warn whether predisposition and way of live are compatible and how unbalanced activities may affect health status. It can help to monitor ongoing therapies, and makes health care decision knowledgeably and thoughtfully.

Biopass is based on our expertise in generating gene expression profiles and in giving sense of these profiles. In practice, the following steps summarize the BioPass® procedure:

- (A) initial time $t = T_0$: PrediGuard quantifies gene expression level and provides some clues on the genetic profiles of its customers
- (B) at $t + 6$ months $= T_6$: PrediGuard quantifies gene expression level and reports on specific correlated genes that eventually present expression out of the range when compared to references and should be followed further on.
- Step (B) is repeated as long as the customer uses BioPass®*'s* service.

BioPass® starts from a blood sample, but in contrast to a standard test, it presents specific features that make the difference:

- it evaluates at once the modulation of 26,000 markers
- it detects very early events (these markers appear before changes in regular proteic or metabolic markers are detected)
- it provides relevant information towards the identification of functional relationships between markers (not identified in individual measurement)

Although BioPass® is still provided to some of our clients (most are VIP), we thought in July 2009 to extend its access to a wider population by promoting the set up of a French Association, "EFGH" (Functional Exploration of the Human Genome ***http://www.asso-efgh.org/download/pdemo.zip***).

EFGH ensures the enrollment of volunteers for a long term period of time and the financing of their gene expression profiles as well as the proper storage of their DNA, serum and urines. For each volunteers, a questionnaire including medical history and details on lifestyle is asked. In addition to a full regular biological assessment, the BioPass® test will be performed twice a year. EFGH aims to give free access of the raw gene expression profiling data to the medical and scientific community collection.

PrediGuard has been mandated by the Association to ensure the realization of the gene expression profiling, the preparation and the storage of the biologic samples as well as the management of the data through the development of a dedicated Internet site. PrediGuard invoices these services for all-in price of 1 000 € per volunteer per year (for the three first years).

Biomarkers

The ultimate goal of PrediGuard is to discover and license new biomarkers. Key of success to discover efficient biomarkers relies not only on its expertise in the area of gene expression analysis but also on its specific strategies.

It is expecting that the main resource of gene expression profiles will be generated via its partnership with the EFGH Association. Furthermore, PrediGuard using its own computational tools, PredictSearch and GeneTracker, will generate its own databases.

It has to be pointed out that instead to analyze individuals that are already facing diseases, the unintended follow up of thousands of presumed healthy individuals should allow to detect very early gene modulation during their lifespan. This modulation may result from either physiological changes such as aging processes or from the onset of a specific disease. Thus, towards the comparison of thousands of expression profiles along with detailed medical history, it will be possible to identify early markers before symptoms occur without any pre-established assumptions.

Moreover, the way to identify biomarkers leads to be focused only on biomarkers that could be detected towards non invasive procedures. Since DNA, serum and urine will be available for each individual, the source or the nature of the biomarker can be different depending on the easiest mode of detection including cost and time consuming issues.

Final validation will be performed at the stage of a licensing agreement with diagnostic companies that includes up-front fees, development milestones and royalties.

PrediGard's scientific and business process has been validated by two collaborations with medical centers. During these collaborations, PrediGuard has identified differential responses to treatment among patients with rheumatoid arthritis or HCV infection.

For rheumatoid arthritis, PrediGuard found that non responder patients express specific genes involved in an alternative pathway that hamper treatment with the therapeutic drug, ENBREL.

For HCV infection, PrediGuard has developed a methodology based on the expression of genes that discriminates within 24 hours responders from non responders before Interferon/Ribavirin treatment.

Both research projects are under validation (additional studies on a larger panel of patients).

In addition, PrediGuard launched an investigation focused on the understanding of the mechanism of action of Chloroquine (known to be efficient against malaria). Recently, PrediGuard was able to identify the molecular basis of its action that could help to monitor chloroquine therapy for patients with autoiummune diseases such as lupus erythematosus.

New fields of research are under investigations (lymphomas, melanomas, prostate and lung cancers, cardiovascular disease, metabolic and CNS disorders).

PrediGuard Milestones

For markers targeting the drug response for rheumatoid arthritis and HCV infection, PrediGuard will start discussion with diagnostic companies within the next 6 months depending on our financing capability.

It is scheduled that from EFGH data, PrediGuard will generate a first set of valuable markers within the next 3 years, receiving at year 4 R&D fundings and milestones payment from leader diagnostic companies.

PrediGuard Partnerships

PrediGuard is engaged in strategic partnerships with several renown hospitals or Cancer Centres such as:Hôpital Américain de Paris, Pitié-Salpétrière (Paris), Ambroise Paré (Marseilles), institute Paoli Calmettes (Marseilles).

These partnerships are crucial for its participation to national and international clinical trials and represent the key of success to ensure the recruitment of volunteers as wells patients with different types of pathologies. .

Biomarker market

The global biomarker market is estimated to be 20.5 billion € by 2014, growing at a CAGR of 19.7% from 2009 to 2014, driven by the high demand for the biomarkers in the field of drug discovery. In addition, the increasing use of biomarkers in clinical services is boosting the overall biomarker service market.

Typically, common agreements in the biomarker business range between 0.1 million € and 5 million € up-front payment from licensing deal, and between 0.5 million € and 10 million € development milestones.

Competitors

A brief overview of the biomarkers market gives rise to a highly diverse picture regarding as to the different strategies developed towards biomarkers identification. Different strategies and technological issues may lead to the identification and the development of biomarkers that have been facilitated with the advent of high throughput technologies at the whole genome scale.

Several companies have already undertaken the commercialization of dedicated genomic

tests specifically designed for several type of cancer.

For instance, Genomic Health with Oncotype DX performs the simultaneous analysis of 21 genes to determine the prognosis value of chemotherapy and to assess the current status of the breast tumors.

Another growing field concerns the genotyping service as a way for companies such as **23andMe** or **NutrEval** to collect data. These data are generated from the detection of SNP (Single Nucleotide Polymorphism), mutations, amplifications/ deletions of DNA. They help to determine the probability of developing disease or of predicting the outcome of a treatment.
Such biomarkers only predict a genetic risk and are not by themselves physiological markers. Looking at the DNA level does not take into account that pathologies depend mainly on the alteration of several genes (most pathologies are multigenic disorders, genes work in an orchestrated manner) and ignores environmental or lifestyle impacts.

Interestingly, it has been announced that 23andMe, the direct-to-consumer genetic testing startup backed by Google Inc. is losing its co-founder, Linda Avey, months after the search giant upped its investment. Linda Avey is leaving to start an Alzheimer's research Association and that the Association would use 23andMe's research technology to test its own patients as they seek Alzheimer's genetic roots.

Postgenomic biomarkers are mainly protein biomarkers and may focus on particular post-translational modifications. Such analysis rely on the screening of protein librairies or antibodies of body fluids (serum, blood, cerebrospinal fluid, urine…) that cannot reach the same scale provided by the genomic tests.
Moreover, protein biomarkers may require analysis of complex mixtures that vary in concentration. The biomarker of interest is more often present at very low quantities in the biologic samples.

However, it has to be kept in mind that:

- "Pathology-related" biomarkers are often elevated in individuals with disease, but they can also be elevated in healthy people who do not have a disease.
- "Pathology-related" biomarkers are not always elevated in people who have a disease.
- "Pathology-related" biomarkers are non-specific, meaning that they may be elevated in a variety of pathologic and non-pathologic conditions, making it difficult to discern why a "pathology-related" biomarker is elevated.

Thus, it is important: (1) to look at multiple biomarkers in combination (called "stacking") since correlations can provide much more information than viewing any single biomarker in isolation, (2) to observe the change of "pathology-related" biomarker levels over time (called "velocity of change"). Large changes are more suggestive of a problem than a single value.

All these issues were the basis on which PrediGuard has developed its strategy.

PrediGuard competitive market strategy

The transcriptional databases issued from the collection of genomic individual follows- up built through the EFGH non profit Association constitute one of the main points of our strategy.

Indeed, biomarkers discovery will rely on the cross comparison of hundreds of transcriptional measurements for any given gene in different contexts: patient suffering from a wide range of pathologies – cancer, cardiovascular diseases, metabolic diseases, neurological diseases,

autoimmune pathologies… - These comparisons are strengthened by the follow up of these individual cases that may be correlated at any time to their health status (disease progression or regression, relapse).

"Because the more you know in advance,

the more it can help"