



# VBC-GENOMICS Bioscience Research GmbH (LLC)

Wolfgang M Schmidt  
Chief Scientific Officer  
VBC-GENOMICS  
Bioscience Research GmbH  
(LLC), Rennweg 95 B,  
A-1030 Vienna, Austria  
Tel: +43 1 796 6572;  
Fax: +43 1 796 6572 321;  
E-mail: research@  
vbc-genomics.com

Founded as a spin-off from the University of Vienna in 1999, VBC-GENOMICS Bioscience Research GmbH (LLC) has rapidly gained a strong position within the Austrian biotech scene, based on its success as a service provider in oligonucleotide synthesis and custom sequencing. In research, the company has focused on the development of diagnostic assays based on microarrays. A technical platform for amplification and analysis of DNA has been established and validated in clinical studies. In addition, the company has developed the world's first protein microarray that is certified as an *in vitro* diagnostic device. This microarray contains allergen components and provides a powerful assay for the profiling of numerous allergy disease-related antigens. The company also markets technological skills and array development expertise to academics and industry.

## Introduction

Launched in March 1999, VBC-GENOMICS Bioscience Research GmbH (LLC) was founded by scientists as a spin-off from an academic institute at the Vienna Biocenter of the University of Vienna. Based on nearly 10 years' experience as a core facility, the company started with well-established services in DNA oligonucleotide synthesis and DNA sequencing. As a well-recognized local service provider, the company had an established clientele and continued to provide custom services in genomics. Their experience ensured a steady income for the young company in times where other biotech start-ups were mainly relying on venture capital. The company's service program has seen constant growth in Austria and expansion to other (primarily neighboring) countries, and was extended in 2002, when VBC-GENOMICS became an Affymetrix GeneChip® service provider. Today, the services sector at VBC-GENOMICS still constitutes a major part of the business and has recently added professional consulting activities in research projects, TaqMan®-based high-throughput genotyping, and custom development projects. The company has seen significant growth during its first 5 years and now has 25 employees.

Driven by an ambitious group of co-founding scientists, VBC-GENOMICS quickly established numerous research projects in the field of microarray technology, with the aim of creating and developing innovative microarray-based diagnostic products. Since then, company scientists have made important progress in developing

innovative surfaces for microarrays suitable for a number of novel applications involving protein interactions and enzymatic activity on solid supports, such as immunoassays or on-chip polymerase chain reaction (PCR).

In the area of DNA microarrays, the company has successfully developed DNA oligo microarray-based tests for measuring gene variation, based on a proprietary on-chip PCR technique that combines the advantages of microarrays with that of conventional PCR. VBC-GENOMICS's majority-owned subsidiary company GENOSENSE Diagnostics GmbH (LLC), which was founded in mid-2001, has introduced these tests to the market, offering genetic testing in combination with profound clinical expertise.

However, perhaps beyond the expectation for a genomics-based company, it was the development of a protein microarray application for the diagnosis of allergic diseases, ISAC® (immuno solid-phase allergen chip), that promised to become the company's first *in vitro* diagnostic array product. In 2002, investors and corporate owners invested ~ €1 million in the product development of ISAC and committed a further ~ €1 million to the market launch of ISAC in 2004.

Furthermore, VBC-GENOMICS has developed and produced the world's first protein microarray to be approved by European Community (EC) regulations as an *in vitro* diagnostic device. This protein microarray, or allergen chip, provides a powerful method for the profiling of a large number of allergy disease-related antigens

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in a single analytical step and is expected to change clinical allergy diagnosis in the course of the next few years.

### A strong core business...

Based on its success as an university-based service provider, VBC-GENOMICS has become the market leader of oligonucleotide synthesis in Austria, and it has achieved a strong position in the field of DNA sequencing. The continuous improvement of its process and product quality (certified since 2003 for standards EN ISO 9001:2000 and EN ISO 13485:2000) has shaped the company into an established service provider in Central Europe that is prepared for the market opportunities in the new member countries of the EU. The company supplies synthetic molecules for a wide range of applications for both academic and industrial clients, with a strong focus on modified DNA as well as RNA oligonucleotides. Synthesis products are distributed by several partner companies, for example, Biozym Scientific GmbH in Germany, Merck spol.s r.o. in Slovakia (a subsidiary of Merck KGaA), and HVD Life Science GmbH in the Middle East.

VBC-GENOMICS is also renowned for its professional DNA sequencing service program based on state-of-the-art capillary sequencing technology and distinguished by its high-quality analysis and excellent customer support. The company's custom sequencing services are highly accepted among academics and the local biotech industry as well.

More recently, the company has gained a reputation as an outstanding Affymetrix GeneChip service provider. GeneChip-based genome-wide expression profiling is offered to academic and industrial customers as a professional full service. A team of application scientists offers a complete range of support – from consulting in study design, experiment planning and lab work, to data analysis, data mining, and preparation of publication. Frequently, customers become partners for close cooperation in joint research projects, providing a wealth of ideas for future activities and developments.

### ...permits dynamic innovation

As a research-oriented biotech company, VBC-GENOMICS has focused on the development of *in vitro* diagnostic applications based on microarray technology. Since their first description in 1995, DNA microarrays have gained importance in many areas of biomedical

research. Scientists at VBC-GENOMICS were quick to envision the specific advantages of microarray technology for future diagnostic devices and have pursued the creation of surface modifications of glass to allow the design of innovative microarray applications. At the time, this constituted a large challenge, since the microarray scene was mainly focused on hybridization applications for RNA expression profiling, while the practical development of novel applications, such as protein microarrays or on-chip PCR, were largely at the conceptual level. At VBC-GENOMICS, company scientists have made significant contributions to the field of biochip technology during the past 4 years. They have not only shown concepts of modern ways in microarray applications, such as protein and peptide chips or 'sequencing-on-chip' strategies, but also have demonstrated numerous examples for relevant applications and have shown the development of both DNA and protein microarray-based test assays for clinically approved testing.

### On-chip PCR in DNA diagnostics

For DNA diagnostic applications, VBC-GENOMICS employs a proprietary method, termed 'on-chip PCR', which is suitable for the amplification and simultaneous characterization of a DNA sample. This technology combines the precision and sensitivity of multiplex DNA amplification with the benefits of microarray-based multi-analyte detection. In contrast to conventional PCR, the reaction is performed directly on the flat surface of a glass slide that holds an array of sequence- or allele-specific solid-phase primers. Thus, in on-chip PCR, amplification and sequence detection are combined within a single step, providing a number of benefits over conventional genotyping techniques [1].

On-chip PCR can be employed to identify single nucleotide polymorphisms (SNPs) in human genomic DNA or to detect and identify pathogens. For example, the company has developed on-chip PCR-based assays for measuring SNPs in human genes with medical relevance [2] or for the detection of bacteria in clinical samples [3], demonstrating the beneficial combination of conventional PCR amplification with microarray technology for the development of simple and rapid DNA diagnostic systems. In the field of DNA diagnostics, two factors play a pivotal role: accuracy and costs. While DNA microarray technology holds promise to save

costs due to the parallel analysis of a high number of diagnostic parameters, the ability of microarrays to possess the high genotyping accuracy that is necessary in routine clinical settings has long been in doubt. However, the availability of rapid and reliable genotyping test systems is a prerequisite for useful entry of genetic testing into modern medicine.

VBC-GENOMICS has made many efforts in order to demonstrate the accuracy and reliability of on-chip PCR-based genotyping assays. To date, the company has developed an assay for measuring allelic variants in the human *MBL2* gene encoding the mannose-binding lectin, an important component of innate immunity of clinical importance in terms of risk of recurrent infections. The assay exploits a number of technical benefits of microarrays, such as a high number of test replicates, and it also uses a proprietary software for automated analysis and genotype assignment. The assay's reliability has been successfully evaluated and the genotyping power in a routine setting has been validated in a large clinical study together with the Children's Hospital at the Medical University of Vienna. In the end, the company has provided one of the scarce examples of an established microarray-based test system ready to be approved as a diagnostic tool according to medical device regulations. The test is available and marketed by GENOSENSE Diagnostics.

As on-chip PCR is a technical platform suitable for analysis of any kind of sequence variation, custom-tailored developments are offered in order to leverage on-chip PCR in future developments. Currently, the company is also seeking appropriate partnering opportunities aiming at improvements and further developments in terms of throughput and establishing on-chip PCR-based integrated devices.

### Protein microarrays for the diagnosis of allergy

It is widely believed that experimental tools for measuring protein levels in a large scale could provide unprecedented opportunities in clinical laboratory diagnosis. While 'classical' methods (such as MALDI/MS or 2D PAGE) in the field of proteomics have proven to be valuable research tools, there is an increasing demand for techniques that enable massive parallel analysis of proteins with high throughput. Shortly after the foundation of the company, scientists at VBC-GENOMICS launched a research and development program aimed at creating a protein

microarray-based solution for this challenge [4]; they have developed microarrays containing panels of recombinant or purified allergen proteins, suitable for multiplexed measuring of allergen-specific IgE directly from sera of allergy patients [5]. A proprietary surface chemistry positively affects the stability of the immobilized proteins and at the same time allows the detection of IgE with high sensitivity and specificity. The method, with regard to assay design and surface chemistry, is protected by a filed patent [101].

Based on the principle of a solid-phase immunoassay, the panel of arrayed allergen molecules allows the highly parallel and miniaturized analysis of IgE titers in minute amounts of a patient's serum. The microarray-based assay has been embedded into a conventional format and is compatible with a broad range of commercially available scanning devices. Based on this approved technology, the company has developed a diagnostic assay, named ISAC, that is suitable for the parallel measurement of allergen-specific IgE-binding patterns from the sera of allergic patients [6]. The application has been refined by establishing a quality-controlled manufacturing process, and ISAC is now certified as an *in vitro* diagnostic product, according to EC regulations (directive 98/79/EC). The supply of the majority of recombinant allergen components used for the production of ISAC is guaranteed through a long-term agreement with the corporate partner company BIOMAY AG, a Vienna-based renowned supplier of allergens and a pioneer in the development of innovative strategies for the treatment of allergic diseases.

In contrast to state-of-the-art methods in allergy diagnosis, ISAC realizes the concept of component-resolved diagnosis of allergic disease by employing only purified allergenic components, either as recombinant proteins or in a natural form. Therefore, ISAC can precisely identify the disease-eliciting molecule and simultaneously uncover potential mono-, oligo- or polysensitization. Thus, by revealing a patient's exact, individual sensitization pattern, ISAC is expected to refine both the decision process leading to the patient's treatment as well as the efficacy of the therapeutic approach and the monitoring progress during the course of a specific immunotherapy [7].

Currently, the company is expanding the ISAC product portfolio for specific settings, such as diagnosis of atopy in children, latex allergy or nut allergy, and refining the assay system in terms of a proprietary bioinformatics tool for

## Highlights

- VBC-GENOMICS is the market leader of oligonucleotide synthesis in Austria, based on its success as an university-based service provider with > 15 years' experience.
- VBC-GENOMICS offers a professional DNA sequencing service.
- The company has a service provider agreement with Affymetrix for the GeneChip product suite. GeneChip-based expression profiling is offered in Europe to academic and industrial customers as a complete package, including consulting, experimental work, bioinformatics, and data mining.
- With its on-chip PCR technology, VBC-GENOMICS has combined the precision and sensitivity of multiplex DNA amplification with the benefits of microarray-based multi-analyte detection. Products are in the pipeline for validation in clinical use and marketed by the majority-owned subsidiary GENOSENSE Diagnostics.
- Based on 5 years of expertise, VBC-GENOMICS also markets its technological skills and know-how in the design and manufacture of custom DNA microarrays for research use in the fields of expression profiling, gene identification and SNP detection.
- With ISAC, VBC-GENOMICS has developed and markets a protein biochip-based *in vitro* diagnostic product that is manufactured in compliance with the medical device regulations of the EU. ISAC is a proprietary application for the allergen-specific determination of antibodies in the sera of allergic patients, and it represents the first protein biochip-based application to have an EC certificate.
- VBC-GENOMICS offers support in custom microarray development projects, supported by a growing portfolio of innovative protein and peptide array applications of its proprietary protein microarray technology, mainly in (but not limited to) the fields of allergic disease and autoimmunity.

automated, unsupervised assay analysis. In the near future, the ISAC test system will be available as a complete solution including an automated processing station, which is being

developed in collaboration with the German company HTI bio-X GmbH. In addition, the company markets its expertise in protein microarray development, as the underlying principle of the ISAC assay has many potential applications in the fields of allergic disease, autoimmunity, and immunology in general.

## Outlook

Protein microarrays for the determination of allergen-specific antibodies developed by VBC-GENOMICS represent a promising example of how modern diagnostic devices will probably change medical diagnosis and the treatment of important diseases in the future. Multiple parallel analysis of a large number of disease-relevant parameters with only minute amounts of patient samples will create a holistic picture of an individual patient's disease state. As a consequence, a hypothesis of the cause of the disease as well as its prognostic development can be formulated from a broad set of data to the benefit of the patient.

Systematic use of multi-analyte microarray applications for screening purposes in risk patients as well as for therapy monitoring will enhance the understanding of the onset and development of a particular disease (e.g., allergy). During the next 5 years, the company expects that the ISAC product panel will play an important role as an advanced diagnostic device in enhancing the process of drug discovery, refining the development in a target-specific manner, and in helping to significantly shorten time-to-patient for novel treatments of allergy.

## Bibliography

1. Huber M, Harwanegg C, Mueller MW, Schmidt WM: On-chip PCR: DNA amplification and analysis on oligonucleotide microarrays. In: *DNA Amplification: Current Technologies and Applications*. Demidov VV, Broude NE (Eds), Horizon Scientific Press, Wymondham, UK (2004) (In Press).
2. Mitterer G, Huber M, Leidinger E *et al.*: Microarray based identification of bacteria in clinical samples by solid-phase PCR of 23S rDNA sequences. *J. Clin. Microbiol.* 42, 1048-1057 (2004).
3. Huber M, Mündlein A, Dornstauder E *et al.*: Accessing single nucleotide polymorphisms in genomic DNA by direct multiplex PCR amplification on oligonucleotide microarrays. *Anal. Biochem.* 303, 25-33 (2002).
4. Harwanegg C, Spitzauer S, Valenta R, Mueller MW, Hiller R: Protein biochips for the profiling of allergen-specific antibodies. In: *Protein Microarrays*. Schena M (Ed.), Jones and Bartlett, Sudbury, MA, USA 221-245 (2004).
5. Hiller R, Laffer C, Harwanegg M *et al.*: Microarrayed allergen molecules: diagnostic gatekeepers for refined allergy treatment. *FASEB J.* 16, 414-416 (2002).
6. Deinhofer K, Sevcik H, Balic N *et al.*: Microarrayed allergens for IgE profiling. *Methods* 32, 249-254 (2004).
7. Harwanegg C, Laffer S, Hiller R *et al.*: Microarrayed recombinant allergens for diagnosis of allergy. *Clin. Exp. Allergy* 33, 7-13 (2003).

## Patent

101. VBC-GENOMICS GmbH: EP-1322960-A1 (2003).