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# The Widely Used Diagnostics "DNA Microarray"-A Review

R. Manoj Kumar
Department of Microbiology and Immunology, New York Medical College,
Valhalla, NY 10595, USA

**Abstract: Problem statement:** DNA microarray technique is one of the latest advances in the field of molecular biology and medicine. It is a multiplex technique used in combination of bioinformatics and statistical data analysis. Since, 1995, the technique offers the possibility of conducting tens or hundreds of thousands of simultaneous hybridizations. **Approach:** This increased experimental efficiency permits high throughput and whole genome expression profiling of pathogens and hosts. **Results:** Microarray technologies are rapidly advancing with numerous applications in gene expression, genotyping, pharmaco-genomics, proteomics and cell biology, in infectious diseases recognizing the causative agent, molecular typing, in studying the interactions between causative agents and host cells, cancer biology, genetics, determining the presence of a pathogen in food samples, to characterize microbial isolates, identifying the presence of virulence factors or microbial resistance genes, to detect microbial mutations associated with resistance to antiretroviral drugs, simultaneously detect and discriminate several viruses, to study the contaminants in cultures, such as mycoplasma, yeasts, fungi, exogenous and endogenous viruses and prions from both animal and human origin so and so forth. **Conclusion:** This article reviewed the applicability of this technique elaborately in some of the important areas of biological sciences.

**Key words:** Microarray, infectious diseases, diagnosis

## INTRODUCTION

DNA microarray technique is one of the latest advances in the field of molecular biology and medicine. It is a multiplex technique used in combination of bioinformatics and statistical data analysis[1]. Bryant and co-researchers[2] reported in his article about microarray that the two developments that are set to revolutionize research and clinical management of infectious diseases are the availability of human genome together with the sequencing of many pathogen genomes and the second as the development of microarray technology.

Microarrays have revolutionized the scientific world from its initial applications to uncover gene expression patterns that are diagnostic and prognostic of cancer to then understanding the interplay between immune responses and disease has been a prime application of this technology. More recent efforts have moved beyond genetic analysis to functional analysis of the molecules involved, including identification of immune-dominant antigens and peptides as well as the role of post-translational glycosylation. Microarray technology is a powerful tool for analyzing the expression profile of thousands of genes in a global way and can be applied to the study of various biological systems.

Availability of huge genome sequence data for the infectious agents and for the human from various databases helps the scientists and the researchers in designing specific and accurate hybridization probes for disease diagnosis[3]. Since the sequence of various microorganisms are available, this level of information and the computational analysis of the described sequences have led to the development of new genomic areas such as: Analysis *in silico*, comparative genomics, functional genomics, transcriptomics, proteomics and pharmaco-genomics[4].

The review article will highlight the selected studies that how microarray has been applied in the study of infectious diseases caused by bacteria, viruses and fungi in human, animals and plants; in cancer diagnosis; in determination of antibiotic resistance; in genetic disorders; identification of biomarkers specific for infectious agents; implications in the field of food sciences and host-pathogen interaction.

**What is microarray?** The theory and background of microarray technology, as well as the technology itself, have been described in detail elsewhere[5,6]. Briefly, microarray consists of an arrayed series of thousands of microscopic spots of DNA oligonucleotides, called features, each containing picomoles of a specific DNA

sequence[7] which is either a short section of a gene or other DNA segments used as probes to hybridize a cDNA or cRNA sample under high-stringency conditions. Probe-target hybridization is usually detected and quantified by fluorescence-based detection of fluorophore-labeled targets to determine relative abundance of nucleic acid sequences in the target[7]. By high specific hybridization of probe nucleic acids with target nucleic acids from clinical samples are allowing effective detection of various diseases with high speed, sensitivity and specificity[3]. The method is able to detect hundreds and thousands of PCR products specific for particular infectious agent[8]: Their resistant gene segments[9] or their virulence factors[10].

Since 1995, DNA microarray finds its way in various fields of molecular biology. This technique has been used efficiently in clinical diagnostics for identifying disease related genes with the help of its biomarkers. It also been used in various other areas of biology like genotyping and determination of disease-relevant genes or agents causing diseases, mutation analysis, screening of Single Nucleotide Polymorphisms (SNPs), detection of chromosome abnormalities and global determination of posttranslational modifications including methylation, acetylation and alternative splicing[3], disease diagnosis, drug discovery and toxicological research[11], in the food industries to detect food-borne pathogenic bacteria, viruses and parasites[1].

**Types of microarrays:** Different types of microarrays have been developed based on their target material, which can be cDNA, mRNA, protein, small molecules, tissues or any other material that allows quantitative analysis which makes them different from each other. Each of these microarrays has several applications in biomedical research. Like, In an mRNA or gene expression profiling experiment the expression levels of thousands of genes are simultaneously monitored to study the effects of certain treatments, diseases and developmental stages on gene expression[12]. Adomas and co-researchers[13] reported that microarray-based gene expression profiling can be used to identify changes in gene expression level in comparison to uninfected cells or tissues. In Chromatin immuno-precipitation on Chip, DNA sequences bound to a particular protein can be isolated by immuno-precipitating that protein (ChIP), these fragments can be then hybridized to a microarray allowing the determination of protein binding site occupancy throughout the genome. SNP detection identifies single nucleotide polymorphism among alleles within or between populations and the other applications of microarrays make use of SNP detection, including Genotyping, forensic analysis, measuring predisposition to disease, identifying drug-candidates, evaluating germline mutations in individuals or somatic mutations in cancers and assessing loss of heterozygosity or genetic linkage analysis[14].

**Applications of microarray:**

**Infectious diseases of human:** From the 20th century to present, Infectious diseases are responsible for major cause of mortality both in human and animal kingdom. Recently, the emergence of infectious diseases has become more serious, as represented by new pathogens such as the viruses causing acquired immune deficiency syndrome, Nipah virus encephalitis, avian influenza, dengue fever and West Nile encephalitis; re-emerging pathogens such as those causing malaria, measles, food-borne pathogens: Methicillin-Resistant (*S. aureus*) (MRSA) and multidrug-resistant (*M. tuberculosis*). Microarray profiling offers many potential advances in diagnostic and therapeutic intervention in human disease because of its unparalleled ability to conduct high-throughput analysis of gene expression. However, limitations of this technique relate in part to issues regarding the various methodologies and experimental designs as well as difficulties in the interpretation of results[15]. Despite these limitations, microarray has been used in efficiently in disease diagnosis.

Lee and colleagues[16] developed a DNA microarray called PathoChip™ for the detection of 44 highly prevalent and fastidious pathogenic bacteria. He used variety of clinical isolates collected from blood, sputum, stool, cerebral spinal fluid, pus and urine to evaluate the technique. Another patented array composing of DNAs amplified with 35 kinds of primers used to amplify 16S-18S sequences, specific antigen, toxin and virulent genes of pathogens causing respiratory infectious disease was developed by Ezaki in 2003, cited by[3]. DNA microarray studies of complex diseases, gene-interaction networks may contain modules of co-regulated or interacting genes that have distinct biological functions. DNA microarray helps in understanding the pathogenesis of these complex diseases which often implicates hundreds of genes. Garaizar and co-researchers[17] in his article summarized the past usage for microbial strain characterizations and the future utilization of DNA microarray technology in epidemiological studies and molecular typing of bacterial pathogens. They also mentioned that a more focused assay concentrating on genomic regions of variability previously detected by genome-wide microarrays will find broad application in routine bacterial epidemiology.

**Bacterial diseases:** In 1998, De Saizieu and co-researchers[18] used oligonucleotide microarrays to measure the relative transcript levels of 100 *Streptococcus pneumoniae* genes during the development of natural competence and during stationary phase[18]. This array is used to identify differences between *M. tuberculosis* and the associated Bacillus Calmette-Guerin vaccine strain[19], to monitor gene expression in *M. tuberculosis* infection of cultured monocytes[20], to identify horizontal gene transfers causing methicillin resistance in *S. aureus*[21] and to show near genetic identity between strains responsible for two separate epidemics of rheumatic fever caused by Group *A. Streptococcus*[22]. Anthony and colleagues in 2000[23] developed a microarray for the identification of bacteria from cultured blood samples from bacteremic patients by using universal PCR primers amplifying bacterial 23S rRNA. Wang and co-workers[24,25] developed a microarray to detect intestinal bacteria from fecal samples by utilizing the 16S rRNA region. Cleven *et al*.[26] reported that instead of exploiting the ribosomal RNA sequences, they employed bacteria species-specific genes like housekeeping genes, virulence factors and antibiotic resistance determinants to study the bacteremia-causing *S. aureus*, *E. coli* and *Pseudomonas aeruginosa*. DNA microarray has been used to study the genetic diversity of *Helicobacter pylori* (*H. pylori*) and their association of gene expression in clinical outcome[4]. Employing this techniques, they report that the alterations in the gene expression of *H. pylori* is related to transcription functions, transduction signals, cell cycle regulation and differentiation, development factors, proliferation/apoptosis balance, expression of membrane proteins and inflammatory response.

**Viral diseases (DNA viruses):** Viruses, the small intracellular pathogens infects almost all living creatures on the earth. DNA microarray techniques is now widely used in the diagnosis of some of the deadly and invasive viral diseases which infects humans, animals, plants and insects. Many researchers used DNA microarray in the field of virology. Human Papilloma Virus (HPV) with more than 120 different types is an important pathogenic virus[27] infecting the hosts skin and mucous membranes[3] and is the main cause of cervical cancer[28]. Li and co-workers[28] reported that by blending multiplex PCR amplification and multiplex hybridization to Liquid Bead Microarray (LBMA) they could detect and identify 25 common HPV genotypes using type-specific primers for HPV E6 and E7 genes in cervical lesions of northern Chinese patients. They further reported that the thus developed HPV-LBMA is a simple, high-throughput method that provides useful information on viral genotype and multiple HPV infections in cervical lesions and studying the genetic information on HPV in cervical specimens by microarray could provide particular benefits in the management of cervical lesions.

Herpes virus group is one of the largest DNA viruses and the family Herpesviridae contains viruses which infects almost all animal species and human. Foldes-Papp and co-researchers used a well-designed and tailored DNA microarray to study the molecular diagnostics of the herpes viruses like Herpes Simplex Virus (HSV)-1, HSV-2, Varicella Zoster Virus (VZV), Epstein-Barr Virus (EBV), Cytomegalovirus (CMV) and HHV-6[29]. An another DNA microarray technology has been developed[30] for the simultaneous detection and species identification of seven human herpes viruses HSV-1, HSV-2, VZV, EBV, CMV, HHV-6A and HHV-6B. Further, Zheng and co- researchers calculated the sensitivity and specificity of the DNA microarray on 61 Cerebrospinal Fluid (CSF) and 132 blood specimens to be 96.2 and 99.3%, respectively. A microarray technique for the detection of all the above said 7 herpes viruses and adeno viruses in co-infected immune-compromised patients have been developed[31]. Jaaskelainen and colleagues[32] developed a multiplex-PCR and microarray-based method for the detection of 8 herpes viruses especially HSV and VZV from herpes virus positive CSF samples.

Another herpes virus, Human Cytomegalovirus (HCMV) is ubiquitous and following resolution of primary productive infection, it persists in the human host by establishing a lifelong latent infection in monocytes and their progenitors[33]. They reported that a microarray-based studies of HCMV have provided useful information about genes that are transcriptionally active during both productive and latent phases of infection on studying with productively infected human foreskin fibroblasts and latently infected primary human myeloid progenitor cells.

**Viral diseases (RNA viruses):** Outbreaks of Highly Pathogenic Avian Influenza (HPAI) virus has caused great economic loss to the poultry industry and resulted in human deaths in Thailand and Vietnam since 2004. Rapid typing and sub-typing of viruses, especially HPAI from clinical specimens, are desirable for taking prompt control measures to prevent spreading of the disease[34]. Yang and co- researchers described a simultaneous approach using microarray to detect and subtype avian influenza virus belonging to H5, H7, H9 subtypes haemagglutinin genes and N1, N2 subtypes neuraminidase genes and they concluded that this array

is a useful diagnostic method[34]. Effective and speedy diagnosis of novel emerging subtypes of influenza viruses is vital for effective global influenza surveillance. Hence a simultaneous subtyping of all influenza A viruses on one chip using a novel DNA microarray has been developed and validated[35]. They could not find any cross-hybridization reaction with other viruses, indicating that the microarray is specific for influenza A viruses and can be undoubtedly be useful for identifying novel influenza A virus subtypes. Mizukami and co-researchers[36] proposed a DNA microarray analysis in the quality control of pandemic and endemic influenza virus whole-virion influenza vaccine, whole virion-particle vaccine and sub-virion vaccine (HA vaccine) and concluded that DNA microarray technology is an informative, rapid and highly sensitive method to evaluate the quality of influenza vaccines.

A panviral DNA microarray platform (Virochip) in the detection of viruses associated with pediatric Respiratory Tract Infections (RTIs) and found virochip to be very efficient on comparison to direct fluorescent antibody and PCR-based testing for the detection of respiratory viruses in 278 nasopharyngeal aspirates and also reported that the virochip is even able to detect viruses not routinely tested for or missed by aforesaid assays[37]. Tiling probes across the VP1 coding region of Vaccine-Derived Poliovirus (VDPV) were used to detect emerging point mutations associated with vaccine virulence and also to detect recombination events[38].

Adaptation through fixation of spontaneous mutations in the viral genome is considered to be one of the important factors that enable recurrent West Nile Virus (WNV) outbreaks in the United States. Hence for effective diagnosis, a microarray assay was developed and optimized for the simultaneous detection of any nucleotide mutations in the entire structural region of WNV in order to facilitate public health surveillance of genetic variation of WNV[39]. Grinev and co-researchers validated Oligonucleotide-based WNV arrays using 23 WNV isolates from the 2002-2005 U.S. epidemics and reported that the array detected unambiguously all mutations in the structural region, serving as a rapid and effective approach for the identification of mutations in the WNV genome.

Hepatitis virus is responsible for chronic liver disease, cirrhosis and hepatocellular carcinoma. Hepatitis B Virus (HBV) and Hepatitis E Virus (HEV) can be detected from a patient's serum through quantitative microarray and microarray employing nanogold-silver stain[40,41]. Oon and co-researchers in 2004 developed a DNA microarray using the human HBV surface antigen unique sequence as DNA probes for detecting human HBV surface antigen mutant in serum samples[3]. Berzsenyi and co reported that microarray profiling has led to a better understanding of the molecular pathogenesis of HBV and Hepatitis C Virus (HCV) in the development of chronic HCV which may prove to have a role in the development of future treatments[15]. Pas and colleagues[42] used a HBV DNA-Chip array which showed a sensitivity and specificity of 97.5 and 97.8%. HCV can be transmitted through blood transfusion. Screening ELISA, the most widely used method for HCV diagnosis, sometimes yields false-positive and false-negative results, hence Kwon and co researchers developed a high diagnostic accuracy of antigen microarray for sensitive detection of hepatitis C virus infection and their method yielded significantly fewer false-positive results and the detection limit was reported to be 1000 times more sensitive than that of the ELISA and concluded that thus developed in expensive method will improve the specificity and sensitivity of large sample volume[43]. Ciccaglione and co-researchers[44] observed that microarray analysis created a common set of cellular genes modulated by different HCV replicon clones. The data generated by microarray provided a comprehensive analysis of alterations in gene expression induced by HCV replication and reveal modulation of new genes potentially useful for selection of antiviral targets.

**Fungal diseases:** There has been a significant advance in the methods and practices used for identification of medically important molds in the 21st century. Normally, molds are identified by colony characters and microscopic examination of their morphology. Currently, DNA-based identification methods are being increasingly employed in many clinical laboratories like, GenProbe assay, microarray-based and Luminex technology[45]. Microarrays have been used to study over 20 species of filamentous fungi that gave a total picture of differences in the transcriptional regulation of genes involved in nutritional pathways, biosynthesis of secondary metabolites and for adaptation[46]. Invasive fungal infections have emerged as a major cause of morbidity and mortality in immune-compromised patients. Leinberger and co-researchers developed a diagnostic microarray for the rapid and simultaneous identification of the 12 most common pathogenic Candida and Aspergillus spp. which was able to detect and clearly identify the fungal pathogens in short time of 4 h[47]. Another oligonucleotide based microarray method was developed[48] to identify 122 strains of fungal pathogens (20 species representing 8 genera) in a single reaction which can discriminate among the

fungal pathogens to the species level. Morrison and colleagues reported a US patented oligonucleotide probes for detecting *Aspergillus* spp. and other filamentous fungi[3]. In another study, Karaolis in 2007 designed hybridization probes against a highly conserved protein in fungi (α-aminoapidate reductase)[3].

**Animal diseases:** Microarray technique is one of the latest diagnostics in veterinary field. Definitive diagnosis of vesicular or vesicular-like lesions in livestock animals presents challenges both for veterinary clinicians and diagnostic laboratories[49]. Even-though the possibility of Foot-and-Mouth Disease Virus (FMDV), Vesicular Stomatitis Virus (VSV) and swine vesicular disease, Vesicular Exanthema of Swine Virus (VESV) is ruled out a definitive diagnosis may remain elusive. They also applied a long oligonucleotide microarray assay to identify viruses that cause vesicular or vesicular-like lesions in livestock animals. They could able to differentiate successfully to genus level of FMDV, VSV, swine vesicular disease virus, VESV, BHV-1, orf virus, pseudocowpox virus, bluetongue virus serotype 1 and Bovine Viral Diarrhea Virus 1 (BVDV1). Leblanc and co-researcher[50] reported a novel method of magnetic bead microarray for the rapid detection and identification of the four recognized species in the pestivirus genus of the Flaviviridae family, i.e., classical swine fever virus, border disease virus, BVDV1 and 2, which allowed specific and sensitive virus detection. They concluded that based on the simplicity of the assay, the protocols for hybridization and magnetic bead detection offer an emerging application for molecular diagnoses in virology that is amenable for use in a modestly equipped laboratory.

**Plant diseases:** Plants viruses are an inherently diverse group that, unlike cellular pathogens. The various diagnostic techniques currently being used for assessing seed, other propagation materials and field samples for the presence of specific viruses include biological indexing, electron microscopy, antibody-based detection, including ELISA, PCR and microarray detection. Microarray detection provides the greatest capability for parallel yet specific testing and can be used to detect individual or combinations of viruses and using current approaches to do so with sensitivity compared to ELISA[51]. Plum Pox Virus (PPV) is the most damaging viral pathogen of stone fruits. Pasquini and co-researchers[52] developed a long 70-mer oligonucleotide DNA microarray capable of simultaneously detecting and genotyping PPV strains and the thus, developed PPV microarray is capable of detecting and identifying all the strains of PPV infected peach, apricot and Nicotiana benthamiana leaves. A microchip detecting potato viruses, PVA, PVS, PVM, PVX, PVY, PLRV, in both single and mixed infections and the chip was also designed to distinguish between the main strains of PVY and PVS, was developed and tested[53,54]. Boonham and colleagues[55] constructed a microarray which is capable of detecting several common potato viruses (PVY, PVX, PVA, PVS) in single and mixed infections.

**Cancer therapy:** Microarray is a powerful tool used widely to characterize tumors and has greatly improved the ability to sub classify tumors according to shared molecular characteristics and clinical behavior. DNA microarray has been developed and applied for the better understanding of the cancer origin and progression. Many researches has been underwent in this competent area in the gene expression profile study of breast cancer[56], in the analysis of multiple gene interaction in cancer[57] gene interaction study in human neuroblastoma[58], protein microarray for the rapid identification of breast cancer autoantibodies[59], as oligonucleotides and cDNA microarray in the gene expression analysis in cervical cancer[60], SNP microarray in genotyping the loss of heterozygosity, genomic copy number changes, DNA methylation alterations, allelic association, cancer predisposition genes, oncogenes and tumor suppressor genes in specific types of tumors[61]. Screening for high-risk human papillomavirus infection remains an important health concern.

**Genetic disorders:** Genetic disorder are obviously caused by the inherited genetic abnormality, such as deletion or duplication of a chromosome, deletion or duplication of a part of chromosome, or a break, translocation, or inversion in the chromosome. Conventional methods used for mutation detection include gel-based sequencing of PCR amplified material, RFLP and SSCP. These sequencing procedures, in spite of their effectiveness, are time-consuming and laborious. Then comes the more effective mutation screening tests like, conformation-sensitive gel electrophoresis[62,63] and capillary electrophoresis[64]. Recently, a DNA microarray has been developed and applied to various diagnostic fields including genetic counseling and SNP screening and typing[3]. The diseases caused by chromosome abnormalities include several types such as Down's syndrome, Edwards syndrome, Patau syndrome, Turner syndrome and Klinefelter syndrome leading to

irreversible physical and mental abnormalities and death and even fetal death[3]. Kang and co-researchers developed a DNA microarray using Bacterial Artificial Chromosome chip (BAC chip) for detecting chromosomal abnormalities of various genetic disorders consisting of Down's syndrome, Patau syndrome, Edward syndrome, Turner syndrome, Klinefelter syndrome, alpha-thalassemia retardation-16, Charcot-Marie-Tooth neuropathy 1A, Cri-du-chat syndrome, hereditary neuropathy with liability to pressure palsies disease, Prader-Willi syndrome, Rubinstein-Taybi syndrome, Williams syndrome and Wolf-Hirschhorn syndrome[3].

**In food sciences:** Microarray analysis of microbial pathogens has potential uses in food safety, agricultural, regulatory, public health and industrial settings[65]. Roy and Sen[66] developed a cDNA microarray technology which may be productively applied to address food safety and also as a tool to analyze food safety with reference to microbial pathogens and genetically modified foods. In a study, Spielbauer and Stahl[67] used DNA and protein array techniques in conjunction with nutrigenomics and nutrigenetics which deals with improving human diet and health and prevent nutrition-related diseases. Kostrzynska and Bachand[1] applied two DNA microarray techniques such as genomic microarrays and oligonucleotide arrays for the detection and identification of pathogens on live food animals and plants as well as in processed food and water which is essential for ensuring the safety of food products for human consumption. Andreoli and colleagues reported a ZIP-code DNA microarray method to overcome the disadvantages of whole- genome DNA-DNA hybridization and also for identifying the contaminating microorganisms in large amounts of foodstuff[3].

Delaquis and co researchers designed DNA microarrays for the differentiation of virulent *E. coli* O157: H7 from nonpathogenic *E. coli* strains isolated from milk[68]. The same team has also designed microarrays for detecting Listeria monocytogenes in milk samples using 16S rRNA-based oligonucleotides that are specific for the pathogen. Wilson and co researchers in 2002[8], in an attempt to detect all three; bacterial, virus and eukaryotes, developed a Multi-Pathogen Identification (MPID) microarray, by which they can identify 18 pathogens (11 bacteria, 5 RNA viruses and 2 eukaryotes) from food samples[68]. Microarray-based detection of viral pathogens could be extremely challenging because of the sequence variability in viruses and the lack of universal primers for PCR amplification[1]. Wang and co researchers[69] developed a microarray with 140 conserved viral genome sequences to screen a diverse range of human respiratory viruses. In another oligonucleotide array developed[70] and is used to detect the common food-borne pathogenic Norovirus in feces. Wang and colleagues[71] developed an oligonucleotide microarray based on genus-species-and subtype-specific probes in conjunction with multiplex PCR to detect and genotype *Entamoeba histolytica*, *Entamoeba dispar*, *Giardia lamblia* and *Cryptosporidium parvum*, all of which are protozoan parasites associated with waterborne disease outbreaks.

**Microarray and biomarkers:** Biomarkers related to a particular disease play an important role in accurate disease diagnosis, proper drug discovery and their toxicity testing. Biomarker discovery using the DNA microarray can be carried out by analyzing global expression levels under different genotypic, phenotypic and environmental conditions, thus allowing large scale candidate identification from the global samples[3,72]. Barnes and researchers[73] reported that by careful application of clinical samples at various stages or conditions to the DNA microarray, the genes that are specifically associated with different disease stages or conditions can be revealed. DNA microarray-based approaches for biomarker discovery have been applied for studying several chronic diseases including diabetes[74], arthritis[73] and cardiovascular disease[75]. Biomarkers for diagnosing chronic autoimmune and inflammatory disorders like systemic lupus erythematosis and rheumatoid arthritis, can be screened by expression profiling in leukocytes[76,77]. Bekal and co-researchers[78] developed a DNA microarray using PCR-amplified products representing *E. coli* virulence genes for use as a diagnostic tool. Van Ijperen and co-researchers[79] conducted virulence typing experiments with a virulence-gene-based DNA microarray and reported that this method to be an efficient and reliable tool for screening *E. coli* isolates. DNA microarrays led to a better understanding of tumor development and identified new prognostic markers[80]. Yoo and co-researchers in their recent article listed the microarrays for Crohn's disease, ulcerative colitis and inflammatory bowel disease diagnosed by using the biomarker genes selected from their gene expression profile[3].

**Drug resistance:** Emerging new and re-emerging old pathogens create profound threats to public health. Diagnostic tests for rapid detection and characterization of microbial agents are critically needed to prevent and respond to disease outbreaks. Drug or antibiotic resistance is one of the most important obstacles faced during bacterial and viral disease control measures. DNA microarray is currently used to identify resistant genes in the infectious agents, helps in developing better therapeutics.

Microarray technique has been used successfully to detect to detect point mutations of pathogens that are associated with antibiotic resistance[81] and oligonucleotide probes for detecting drug resistance[82]. An oligonucleotide array was used to detect mutant alleles of the M. tuberculosis rpoB gene, which are known to confer resistance to rifampicin[83,84], against dapsone and ofloxacin resistance[84]. A high density NimbleGen microarray system targeting microbial antibiotic resistance and virulence mechanisms, employing *E. coli* strains K12 and CFT073, *Enterococcus faecalis* and *S. aureus* have been developed[85] which can be used to obtain important data about the pathogenic potential and drug resistance profiles of unknown organisms in environmental samples.

Diagnostic microarray was used to characterize a collection of MRSA isolates from hospital cases by detecting variants that differed mainly in the carriage of additional resistance determinants and certain virulence-associated genes[86]. Spence and co-researchers[87] developed and validated a novel, cost-effective multiwell microarray which targets 84 genes of *S. aureus*, including species-specific, antibiotic resistance, toxin and other virulence-associated genes of 13 different isolates of *S. aureus* simultaneously. They further characterized 43 *S. aureus* isolates by microarray and pulsed-field gel electrophoresis to differentiate between isolates representative of a spectrum of methicillin-susceptible, methicillin-resistant, community-acquired and vancomycin-resistant *S. aureus*. A glass-based microarray was developed[88] to detect 11 antimicrobial resistance genes that confer resistance to aminoglycosides, tetracyclines, sulfonamides and chloramphenicols in *Salmonella* isolates with high sensitivity. Influenza A viruses has the ability to rapidly mutate and become resistant to the commonly used therapeutics hence, Townsend and co-researchers[89] designed a cost-effective low-density microarray called the Antiviral Resistance-chip (AVR-chip) with the advantage of functional genomics which could be able to detect mutations in the M2 protein associated with adamantane resistance. The AVR-Chip provided a method for rapidly screening influenza viruses for adamantane sensitivity, which could be easily extended to detect resistance to other chemotherapeutics.

## CONCLUSION

Microarray technology is based on the well-established and highly exploited principle of nucleic acid hybridization. The technique offers the possibility of simultaneously conducting tens or hundreds of thousands of simultaneous hybridizations. This increased experimental efficiency permits high throughput and whole genome expression profiling of pathogens and hosts. Microarray technologies are rapidly advancing with numerous applications in Medicine, genomics, proteomics, pharmaco-genomics, molecular biology, infectious diseases, food industry, chemotherapy, antibiotic resistance and so on. While the use of microarray in the investigation of infectious diseases is still in its infancy, new innovations in this emerging technology will throw more light in understanding the molecular basis of infectious agents and the diseases. Microarray-based diagnostics is being developed in many countries and still new ideas are being incorporated into the assays to increase their versatility. Whole of the scientific community have great hope for this technique to find its implications in various aspects of human mankind.

## REFERENCES

1. Kostrzynska, M. and A. Bachand, 2006. Application of DNA microarray technology for detection, identification and characterization of food-borne pathogens. Can. J. Microbiol., 52: 1-8. http://www.ncbi.nlm.nih.gov/pubmed/16541153
2. Bryant, P.A., D. Venter, R. Robins-Browne and N. Curtis, 2004. Chips with everything: DNA microarrays in infectious diseases. The Lancet Dis., 4: 100-111. http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(04)00930-2/fulltext
3. Yoo, S.M., H.C. Jong, S.Y. Lee and N.C. Yoo, 2009. Applications of DNA microarray in disease diagnostics. J. Microbiol. Biotechnol., 19: 51-54. DOI: 10.4014/jmb.0803.226
4. Morales, E.M.R., G.D. Sapién and A. Cravioto, 2003. The use of microarrays for studying the pathogenesis of helicobacter pylori. Rev. Latinoam. Microbiol., 45: 24-29. http://www.ncbi.nlm.nih.gov/pubmed/17061518
5. Ferea, T.L. and P.O. Brown, 1999. Observing the living genome. Curr. Opin. Genet. Dev., 9: 715-722. http://www.ncbi.nlm.nih.gov/pubmed/10607618
6. Lipshutz, R.J., S.P. Fodor, T.R. Gingeras and D.J. Lockhart, 1999. High density synthetic oligonucleotide arrays. Nat. Genet., 21: 20-24. http://www.ncbi.nlm.nih.gov/pubmed/9915496
7. Schena, M., D. Shalon, R.W. Davis and P.O. Brown, 1995. Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science, 270: 467-470. DOI: 10.1126/science.270.5235.467

8. Wilson, W.J., C.L. Strout, T.Z. DeSantis, J.L. Stilwell, A.V. Carrano and G.L. Andersen, 2002. Sequence-specific identification of 18 pathogenic microorganisms using microarray technology. Mol. Cell. Probes, 16: 119-127. http://www.ncbi.nlm.nih.gov/pubmed/12030762?dopt=Abstract
9. Call, D.R., M.K. Bakko, M.J. Krug and M.C. Roberts, 2003. Identifying antimicrobial resistance genes with DNA microarrays. Antimicrob. Agents Chemother., 47: 3290-3295. http://www.ncbi.nlm.nih.gov/pubmed/14506043
10. Chizhikov, V., A. Rasooly, K. Chumakov and D.D. Levy, 2001. Microarray analysis of microbial virulence factors. Applied Environ. Microbiol., 67: 3258-3263. http://www.ncbi.nlm.nih.gov/pubmed/11425749
11. Iida, K. and I. Nishimura, 2002. Gene expression profiling by DNA microarray technology. Crit. Rev. Oral Biol. Med., 13: 35-50. http://crobm.iadrjournals.org/cgi/content/full/13/1/35
12. Jayapal, M. and A.J. Melendez, 2006. DNA Microarray technology for target identification and validation. Clin. Exp. Pharmacol. Physiol., 33: 496-503. http://www3.interscience.wiley.com/journal/118729132/abstract
13. Adomas, A., G. Heller, A. Olson, J. Osborne and M. Karlsson, 2008. Comparative analysis of transcript abundance in Pinus sylvestris after challenge with a saprotrophic, pathogenic or mutualistic fungus. Tree Physiol., 28: 885-897. http://www.ncbi.nlm.nih.gov/pubmed/18381269
14. Hacia, J.G., J.B. Fan, O. Ryder, L. Jin, K. Edgemon and G. Ghandour *et al*., 1999. Determination of ancestral alleles for human single-nucleotide polymorphisms using high-density oligonucleotide arrays. Nat. Genet., 22: 164-167. DOI: 10.1038/9674
15. Berzsenyi, M.D., S.K. Roberts and M.R. Beard, 2006. Genomics of hepatitis B and C infections: Diagnostic and therapeutic applications of microarray profiling. Antivir. Ther., 11: 541-552. http://www.ncbi.nlm.nih.gov/pubmed/16964821
16. Lee, Y., E.K. Lee, Y.W. Cho, T. Matsui, I.C. Kang, T.S. Kim and M.H. Han, 2003. Proteo chip: A highly sensitive protein microarray prepared by a novel method of protein immobilization for application of protein-protein interaction studies.. Proteomics, 3: 2289-2304. http://www.ncbi.nlm.nih.gov/pubmed/14673779
17. Garaizar, J., A. Rementeria and S. Porwollik, 2006. DNA microarray technology: A new tool for the epidemiological typing of bacterial pathogens? FEMS. Immunol. Med. Microbiol., 47: 178-189. http://www3.interscience.wiley.com/journal/118583288/abstract
18. De Saizieu, A., U. Certa, J. Warrington, C. Gray, W. Keck and J. Mous, 1998. Bacterial transcript imaging by hybridization of total RNA to oligonucleotide arrays. Nat. Biotechnol., 16: 45-48. http://www.nature.com/nbt/journal/v16/n1/abs/nbt0198-45.html
19. Behr, M.A., M.A. Wilson, W.P. Gill, H. Salamon, G.K. Schoolnik, S. Rane and P.M. Small, 1999. Comparative genomics of BCG vaccines by whole-genome DNA microarray. Science, 284: 1520-1523. http://www.ncbi.nlm.nih.gov/pubmed/10348738
20. Mangan, J.A., I.M. Monahan, M.A. Wilson, D. Schnappinger, G.K. Schoolnik and P.D. Butcher, 1999. The expression profile of Mycobacterium tuberculosis infecting the human monocytic cell line THP-1 using whole genome microarray analysis. Nat. Genet., 23: 61-61. http://www.nature.com/ng/journal/v23/n3s/full/ng1199supp_61c.html
21. Fitzgerald, J.R., D.E. Sturdevant, S.M. Mackie, S.R. Gill and J.M Musser, 2001. Evolutionary genomics of *Staphylococcus aureus*: Insights into the origin of methicillin-resistant strains and the toxic shock syndrome epidemic. Proc. Natl. Acad. Sci. USA., 98: 8821-8826. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=11447287
22. Smoot, J.C., K.D. Barbian, J.J. Van Gompel, L.M. Smoot and M.S. Chaussee *et al*., 2002. Genome sequence and comparative microarray analysis of serotype M18 group a streptococcus strains associated with acute rheumatic fever outbreaks. Proc. Natl. Acad. Sci. USA., 99: 4668-4673. http://www.ncbi.nlm.nih.gov/pubmed/11917108
23. Anthony, R.M., T.J. Brown and G.L. French, 2000. Rapid diagnosis of bacteremia by universal amplification of 23S ribosomal DNA followed by hybridization to an oligonucleotide array. J. Clin. Microbiol., 38: 781-788. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=10655385
24. Wang, R.F., M.L. Beggs, L.H. Robertson and C.E. Cerniglia, 2002. Design and evaluation of oligonucleotide-microarray method for the detection of human intestinal bacteria in fecal samples. FEMS. Microbiol. Lett., 213: 175-182. http://www.ncbi.nlm.nih.gov/pubmed/12167534

25. Wang, R.F., S.J. Kim, L.H. Robertson and C.E. Cerniglia, 2002. Development of a membrane-array method for the detection of human intestinal bacteria in fecal samples. Mol. Cell. Probes, 16: 341-350. http://www.ncbi.nlm.nih.gov/pubmed/12477438
26. Cleven, B.E., M. Palka-Santini, J. Gielen, S. Meembor, M. Krönke and O. Krut, 2006. Identification and characterization of bacterial pathogens causing bloodstream infections by DNA microarray. J. Clin. Microbiol., 44: 2389-2397. http://www.ncbi.nlm.nih.gov/pubmed/16825354
27. Min, W., M. Wen-Li, Z. Bao, L. Ling, S. Zhao-Hui and Z.O. Wen-Ling, 2006. Oligonucleotide microarray with RD-PCR labeling technique for detection and typing of human papillomavirus. Curr. Microbiol., 52: 204-209. http://www.ncbi.nlm.nih.gov/pubmed/16479359
28. Li, Y., Y. Wang, C. Jia, Y. Ma, Y. Lan and S. Wang, 2008. Detection of human papillomavirus genotypes with liquid bead microarray in cervical lesions of northern Chinese patients. Cancer Genet. Cytogenet., 182: 12-17. http://www.ncbi.nlm.nih.gov/pubmed/18328945
29. Foldes-Papp, Z., R. Egerer, E. Birch-Hirschfeld, H.M. Striebel, U. Demel, G.P. Tilz and P. Wutzler, 2004. Detection of multiple human herpes viruses by DNA microarray technology. Mol. Diagn., 8: 1-9. http://www.ncbi.nlm.nih.gov/pubmed/15230636
30. Zheng, Z.B., Y.D. Wu, X.L. Yu and S.Q. Shang, 2008. DNA microarray technology for simultaneous detection and species identification of seven human herpes viruses. J. Med. Virol., 80: 1042-1050. http://www3.interscience.wiley.com/journal/118821250/abstract?CRETRY=1&SRETRY=0
31. Muller, R., A. Ditzen, K. Hille, M. Stichling, R. Ehricht, T. Illmer, G. Ehninger and J. Rohayem, 2008. Detection of herpesvirus and adenovirus co-infections with diagnostic DNA-microarrays. J. Virol. Methods, 155: 161-166. http://www.ncbi.nlm.nih.gov/pubmed/19022297
32. Jaaskelainen, A.J., H. Piiparinen, M. Lappalainen and A. Vaheri, 2008. Improved multiplex-PCR and microarray for herpesvirus detection from CSF. J. Clin. Virol., 42: 172-175. http://www.journalofclinicalvirology.com/article/S1386-6532(08)00035-8/abstract
33. Slobedman, B. and A.K. Cheung, 2008. Microarrays for the study of viral gene expression during human cytomegalovirus latent infection. Methods Mol. Med., 141: 153-175. http://www.ncbi.nlm.nih.gov/pubmed/18453089
34. Yang, Z., X. Wang, L. Tian, Y. Wang and H. Chen, 2008. Typing and subtyping avian influenza virus using DNA microarrays. Wei Sheng Wu Xue Bao, 48: 935-940. http://www.ncbi.nlm.nih.gov/pubmed/18837373
35. Han, X., X. Lin, B. Liu, Y. Hou, J. Huang, S. Wu, J. Liu, L. Mei, G. Jia and Q. Zhu, 2008. Simultaneously subtyping of all influenza A viruses using DNA microarrays. J. Virol. Methods, 152: 117-121. PMID: 18639939.
36. Mizukami, T., J. Imai, I. Hamaguchi, M. Kawamura, H. Momose, S. Naito, J. Maeyama, A. Masumi, M. Kuramitsu, K. Takizawa, N. Nomura, S. Watanabe and K. Yamaguchi, 2008. Application of DNA microarray technology to influenza A/vietnam/1194/2004 (H5N1) vaccine safety evaluation. Vaccine, 26: 2270-2283. PMID: 18374459
37. Chiu, C.Y., A. Urisman, T.L. Greenhow, S. Rouskin, S. Yagi, D. Schnurr, C. Wright, D.L. Drew, D. Wang, P.S. Weintrub, J.L. Derisi and D. Ganem, 2008. Utility of DNA microarrays for detection of viruses in acute respiratory tract infections in children. J. Pediatr., 153: 76-83. PMID: 18571541
38. Cherkasova, E., M. Laassri, V. Chizhikov, E. Korotkova, E. Dragunsky, V.I. Agol and K. Chumakov, 2003. Microarray analysis of evolution of RNA viruses: Evidence of circulation of virulent highly divergent vaccine-derived polioviruses. Proc. Nat. Acad. Sci. USA., 100: 9398-403. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=12878723
39. Grinev, A., S. Daniel, M. Laassri, K. Chumakov, V. Chizhikov and M. Rios, 2008. Microarray-based assay for the detection of genetic variations of structural genes of West Nile virus. J. Virol. Methods, 154: 27-40. PMID: 18930080
40. Kawaguchi, K., S. Kaneko, M. Honda, F.H. Kawai, S. Yukihiro and K. Kenichi, 2003. Detection of hepatitis B virus DNA in sera from patients with chronic hepatitis B virus infection by DNA microarray method. J. Clin. Microbiol., 41: 1701-1704. http://jcm.asm.org/cgi/reprint/41/4/1701
41. Liu, H.H., X. Cao, Y. Yang, M.G. Liu and Y.F. Wang, 2006. Array-based nano-amplification technique was applied in detection of hepatitis E virus. J. Biochem. Mol. Biol., 39: 247-252. http://www.jbmb.or.kr/fulltext/jbmb/view.php?vol=39&page=247

42. Pas, S.D., N. Tran, R.A. de Man, C. Burghoorn-Maas, G. Vernet and H.G. Niesters, 2008. Comparison of reverse hybridization, microarray and sequence analysis for genotyping hepatitis B virus. J. Clin. Microbiol., 46: 1268-1273. PMID: 18287321
43. Kwon, J.A., H. Lee, K.N. Lee, K. Chae, S. Lee, D.K. Lee and S. Kim, 2008. High diagnostic accuracy of antigen microarray for sensitive detection of hepatitis C virus infection. Clin. Chem., 54: 424-428. PMID: 18223133
44. Ciccaglione, A.R., C. Marcantonio, E. Tritarelli, P. Tataseo and A. Ferraris *et al*., 2008. Microarray analysis identifies a common set of cellular genes modulated by different HCV replicon clones. BMC Genomics, 30: 309-309. PMID: 18590516
45. Balajee, S.A., L. Sigler and M. Brandt, 2007. DNA and the classical way: Identification of medically important molds in the 21st century. Med. Mycol., 45: 475-490. http://www.informaworld.com/smpp/content~db=all?content=10.1080/13693780701449425
46. Breakspear, A. and M.T. Momany, 2007. The first fifty microarray studies in filamentous fungi. Microbiology, 153: 7-15. http://mic.sgmjournals.org/cgi/content/full/153/1/7?view=long&pmid=17185530
47. Leinberger, D.M., U. Schumacher, I.B. Autenrieth and T.T. Bachmann, 2005. Development of a DNA microarray for detection and identification of fungal pathogens involved in invasive mycoses. J. Clin. Microbiol., 43: 4943-4953. http://jcm.asm.org/cgi/content/full/43/10/4943?view=long&pmid=16207946
48. Huang, A., J.W. Li, Z.Q. Shen, X.W. Wang and M. Jin, 2006. High-throughput identification of clinical pathogenic fungi by hybridization to an oligonucleotide microarray. J. Clin. Microbiol., 44: 3299-3305. http://jcm.asm.org/cgi/content/full/44/9/3299?view=long&pmid=16954264
49. Jack, P.J., R.N. Amos-Ritchie, A. Reverter, G. Palacios and P.L. Quan *et al*., 2009. Microarray-based detection of viruses causing vesicular or vesicular-like lesions in livestock animals. Vet. Microbiol., 133: 145-153. PMID: 18621489
50. Leblanc, N., J. Gantelius, J.M. Schwenk, K. Stahl, J. Blomberg, H. Andersson-Svahn and S. Belák, 2009. Development of a magnetic bead microarray for simultaneous and simple detection of four pestiviruses. J. Virol. Methods, 155: 1-9. PMID: 18514335
51. Boonham, N., J. Tomlinson and R. Mumford, 2007. Microarrays for rapid identification of plant viruses. Annu. Rev. Phytopathol., 45: 307-328. http://www.ncbi.nlm.nih.gov/pubmed/17691887
52. Pasquini, G., M. Barba, A. Hadidi, F. Faggioli and R. Negri *et al*., 2008. Oligonucleotide microarray-based detection and genotyping of Plum pox virus. J. Virol. Methods, 147: 118-126. PMID: 17920703
53. Bystricka, D., O. Lenz, I. Mraz, L. Piherova, S. Kmoch and M. Sip, 2005. Oligonucleotide-based microarray: A new improvement in microarray detection of plant viruses. J. Virol. Methods, 128: 176-182. PMID: 15927276
54. Bystricka, D., O. Lenz, I. Mraz, P. Dedic and M. Síp, 2003. DNA microarray: parallel detection of potato viruses. Acta Virol., 47: 41-44. PMID: 12828343
55. Boonham, N., K. Walsh, P. Smith, K. Madagan, I. Graham and I. Barker, 2003. Detection of potato viruses using microarray technology: Towards a generic method for plant viral disease diagnosis. J. Virol. Methods, 108: 181-187. PMID: 12609685
56. Ramanathan, S.U. and T. Rajkumar, 2007. DNA microarray and breast cancer-a review. Int. J. Hum. Genet., 7: 49-56. PMID: 18311903
57. Virtanen, C. and J. Woodgett, 2008. Clinical uses of microarrays in cancer research. J. Methods Mol. Med., 141: 87-113. PMID: 18453086
58. Ohira, M., S. Oba, Y. Nakamura, T. Hirata, S. Ishii and A. Nakagawara, 2005. A review of DNA microarray analysis of human neuroblastomas. Cancer Lett., 228: 5-11. PMID: 15936139
59. Andersen, P.S., C. Jespersgaard, J. Vuust, M. Christiansen and L.A. Larsen, 2003. Capillary electrophoresis-based single strand DNA conformation analysis in high-throughput mutation screening. Hum. Mutat., 21: 455-465. http://www3.interscience.wiley.com/journal/104086641/abstract
60. Chao, A., T.H. Wang and C.H. Lai, 2007. Overview of microarray analysis of gene expression and its applications to cervical cancer investigation. Taiwan J. Obstet. Gynecol., 46: 363-373. PMID: 18182341
61. Mao, X., B.D. Young and Y.J. Lu, 2007. The application of single nucleotide polymorphism microarrays in cancer research. Curr. Genomics, 8: 219-228. http://www.ncbi.nlm.nih.gov/pubmed/18645599
62. Acquila, M., F. Bottini, A. Valetto, D. Caprino, P.G. Mori and M.P. Bicocchi, 2001. A new strategy for prenatal diagnosis in a sporadic haemophilia B family. Haemophilia, 7: 416-418. http://www3.interscience.wiley.com/journal/120825664/abstract

63. Korkko, J., I. Kaitila, L. Lonnqvist, L. Peltonen and L. Ala-Kokko, 2002. Sensitivity of conformation sensitive gel electrophoresis in detecting mutations in Marfan syndrome and related conditions. J. Med. Genet., 30: 34-41. http://www.ncbi.nlm.nih.gov/pubmed/11826022
64. Anderson, K.S., N. Ramachandran, J. Wong, J.V. Raphael and E. Hainsworth, 2008. Application of protein microarrays for multiplexed detection of antibodies to tumor antigens in breast cancer. J. Proteome Res., 7: 1490-1499. http://pubs.acs.org/doi/abs/10.1021/pr700804c
65. Rasooly, A. and K.E. Herold, 2008. Food microbial pathogen detection and analysis using DNA microarray technologies. Foodborne Pathog. Dis., 5: 531-550. http://www.ncbi.nlm.nih.gov/pubmed/18673074
66. Roy, S. and C.K. Sen, 2006. cDNA microarray screening in food safety. Toxicology, 221: 128-133. PMID: 16466843
67. Spielbauer, B. and F. Stahl, 2005. Impact of microarray technology in nutrition and food research. Mol. Nutr. Food Res., 49: 908-917. PMID: 16189797
68. Delaquis, S., S. Stewart, S. Cazaux and P. Toivonen, 2002. Survival and growth of listeria monocytogenes and *Escherichia coli* O157:H7 in ready-to-eat iceberg lettuce washed in warm chlorinated water. J. Food Prot., 65: 459-464. http://www.ncbi.nlm.nih.gov/pubmed/14672214
69. Wang, D., L. Coscoy, M. Zylberberg, P.C. Avila and H.A. Boushey, 2002. Microarray-based detection and genotyping of viral pathogens. Proc. Natl. Acad. Sci. USA., 99: 15687-15692. http://www.ncbi.nlm.nih.gov/pubmed/12429852
70. Pagotto, F., N. Corneau, K. Karthikeyan and S. Bidawid, 2004. Current advances in Norovirus: From foods to microarrays. Proceedings of the Federal Food Safety and Nutrition Research Meeting. Oct. 3-5, Kanata, Ontario, Canada, pp: 80.
71. Wang, Z., G.J. Vora and D.A. Stenger, 2004. Detection and genotyping of entamoeba histolytica, entamoeba dispar, giardia lamblia and cryptosporidium parvum by oligonucleotide microarray. J. Clin. Microbiol., 42: 3262-3271. http://jcm.asm.org/cgi/content/full/42/7/3262?view=long&pmid=15243091
72. Wang, X.W., L. Zhang, L.Q. Jin, M. Jin and Z.Q. Shen, 2007. Development and application of an oligonucleotide microarray for the detection of food-borne bacterial pathogens. Appl. Microbiol. Biotechnol., 76: 225-233. http://www.ncbi.nlm.nih.gov/pubmed/17492283
73. Barnes, M.G., B.J. Aronow, L.K. Luyrink, M.B. Moroldo, P. Pavlidis and M.H. Passo, 2004. Gene expression in juvenile arthritis and spondyloarthropathy: Pro-angiogenic ELR+chemokine genes relate to course of arthritis. Rheumatology, 43: 973-979. PMID: 15150433
74. Baelde, H.J., M. Eikmans, P.P. Doran, D.W. Lappin, E. De Heer and J.A. Bruijn, 2004. Gene expression profiling in glomeruli from human kidneys with diabetic nephropathy. Am. J. Kidney Dis., 43: 636-650. http://www.ncbi.nlm.nih.gov/pubmed/15042541
75. McNeil, M.M., S.L. Nash, R.A. Hajjeh, M.A. Phelan and L.A. Conn *et al*., 2001. Trends in mortality due to invasive mycotic diseases in the United States, 1980-1997. Clin. Infect. Dis., 33: 641-647. http://www.journals.uchicago.edu/doi/full/10.1086/322606?cookieSet=1
76. Crow, M.K. and J. Wohlgemuth, 2003. Microarray analysis of gene expression in lupus. Arthritis Res. Ther., 5: 279-287. http://www.ncbi.nlm.nih.gov/pubmed/14680503
77. Crow, M.K., K.A. Kirou and J. Wohlgemuth, 2003. Microarray analysis of interferon-regulated genes in SLE. Autoimmunity, 36: 481-490. PMID: 14984025
78. Bekal, S., R. Brousseau, L. Masson, G. Prefontaine, J. Fairbrother and J. Harel, 2003. Rapid identification of *Escherichia coli* pathotypes by virulence gene detection with DNA microarrays. J. Clin. Microbiol., 41: 2113-2125. http://jcm.asm.org/cgi/content/full/41/5/2113?view=long&pmid=12734257
79. Van Ijperen, C., P. Kuhnert, J.Frey and J.P. Clewley, 2002. Virulence typing of *Escherichia coli* using microarrays. Mol. Cell. Probes, 16: 371-378. PMID: 12477441
80. Gillet, J.P., F. De Longueville and J. Remacle, 2006. DualChip microarray as a new tool in cancer research. Expert. Rev. Mol. Diagn., 6: 295-306. PMID: 16706734
81. Booth, S.A., M.A. Drebot, I.E. Martin and L.K. Ng, 2003. Design of oligonucleotide arrays to detect point mutations: Molecular typing of antibiotic resistant strains of *Neisseria gonorrhoeae* and hantavirus infected deer mice. Mol. Cell. Probes, 17: 77-84. PMID: 12788028
82. Gingeras, T.R., R. Higuchi, L.J. Kricka, Y.M. Lo and C.T. Wittwer, 2005. Fifty years of molecular (DNA/RNA) diagnostics. Clin Chem., 51: 661-671. PMID: 15650028

83. Troesch, A., H. Nguyen, C.G. Miyada, S. Desvarenne, T.R. Gingeras and P.M. Kaplan, 1999. Mycobacterium species identification and rifampin resistance testing with high-density DNA probe arrays. J. Clin. Microbiol., 37: 49-55. http://jcm.asm.org/cgi/content/full/37/1/49?view=long&pmid=9854063
84. Matsuoka, M., K.S. Aye, K. Kyaw, E.V. Tan and M.V. Balagon *et al*., 2008. A novel method for simple detection of mutations conferring drug resistance in Mycobacterium leprae, based on a DNA microarray and its applicability in developing countries. J. Med. Microbiol., 57: 1213-1219. PMID: 18809547
85. Jaing, C., S. Gardner, K. McLoughlin, N. Mulakken, M. Alegria-Hartman, P. Banda, P. Williams, P. Gu, M. Wagner, C. Manohar and T.A. Slezak, 2008. A functional gene array for detection of bacterial virulence elements. PLoS One, 3: 2163. http://www.ncbi.nlm.nih.gov/pubmed/18478124
86. Monecke, S., L. Jatzwauk, S. Weber, P. Slickers and R. Ehricht, 2008. DNA microarray-based genotyping of methicillin-resistant Staphylococcus aureus strains from Eastern Saxony. Clin. Microbiol. Infect., 14: 534-545. PMID: 18373691
87. Spence, R.P., V. Wright, D.A. Ala-Aldeen, D.P. Turner, K.G. Wooldridge and R. James, 2008. Validation of virulence and epidemiology DNA microarray for identification and characterization of staphylococcus aureus isolates. J. Clin. Microbiol., 46: 1620-1627. http://jcm.asm.org/cgi/content/full/46/5/1620?view=long&pmid=18287310
88. Ma, M., H. Wang, Y. Yu, D. Zhang and S. Liu, 2007. Detection of antimicrobial resistance genes of pathogenic Salmonella from swine with DNA microarray. J. Vet. Diagn. Invest., 19: 161-167. PMID: 17402610
89. Townsend, M.B., J.A. Smagala, E.D. Dawson, V. Deyde, L. Gubareva, A.I. Klimov, R.D. Kuchta and K.L. Rowlen, 2008. Detection of adamantane-resistant influenza on a microarray. J. Clin. Virol., 42: 117-123. PMID: 18299250