FONDAZIONE ISTITUTO ITALIANO DI TECNOLOGIA

A TECHNOLOGY TEASER

PROBE KIT FOR DETECTING A SINGLE STRAND NUCLEOTIDE

Released on July 2014

HEALTH TECHNOLOGIES

Istituto Italiano di Tecnologia – Mission and History

The Foundation is intended to promote Italy's technological development and advanced education, consistent with national policies for scientific and technological development, thus strengthening the national production system.
For this purpose, the Foundation:
- helps and accelerates the development, within the national research system, of scientific and technological skills able to facilitate state of the art technological advancements of the national production system;
- develops innovative methods and know-how, in order to facilitate new high-level practices and positive competitive mechanisms in the field of national research;
- promotes and develops scientific and technological excellence, both directly, through its multi-disciplinary research laboratories, and indirectly, through a wide collaboration with national and international laboratories and research teams;
- carries out advanced training programs as a part of wider multi-disciplinary projects and programs;
- fosters a culture based on sharing and valuing results, to be used in order to improve production and for welfare-related purposes, both internally and in relation to the entire national research system;
- creates technological understanding about components, methods, processes and techniques to be used for the implementation and interconnection of innovative products and services, in strategic areas for the competitiveness of the national production system;
- pools research scientists operating in various research institutes and establishes cooperation agreements with high-level, specialized centers;
- promotes interactions between basic research and applied research facilities, encouraging experimental development;
- spreads transparent, merit-based selection mechanisms for research scientists and projects, in compliance with globally approved and established criteria.

CONTENTS

EXECUTIVE SUMMARY

The nascent but steadily growing field of miRNA research has been one of the most prolific contributors to modern medicine in recent times. Still at the developmental stage, miRNA research has helped those in the medical sector in understanding the dynamics of various diseases from a different perspective. Notable discoveries and rapid progress in the past few years provide the hope that miRNAs will in the near future have great potential in the diagnosis and treatment of many diseases.

However, traditional assays require labour-intensive and time-consuming protocols. The increase of the demand of nucleic testing entails the need for rapid detection strategies, in particular, assays that does not require separation, amplification, and other related operations are highly desirable. This is the purpose of the IIT technologies.

These technologies represent a unique chance for companies active in the markets of nucleic acid testing and microRNA. IIT assets appear well positioned for an out-licensing strategy, providing the licensee partner with the ability to take care of the late stage development, CE certification, scale-up and production process. The licensee should guarantee a high probability of market success based on consolidated marketing & distribution organization. A typical licensing strategy based on entry fee and subsequent royalties on net sales can be envisaged.

In the following paragraphs an IP outlook and a description of the IIT technology are available. Furthermore, the IIT Business and Financial Analysis Office (BFAO) implemented a market analysis and a competitive analysis highlighting the profiles of the most active industrial players in the sector.

INTELLECTUAL PROPERTY

PCT International Application #	PCT/IB2013/061377 - 27 December 2013
Priority Application #	IT 102012902113955 (TO2012A001154) - 27 December 2012
Regional Patent Applications filed	**US** 14/655276**, EP** 13831873.8
Applicant	Fondazione Istituto Italiano di Tecnologia
Inventors	Causa Filippo, Battista Edmondo, Aliberti Anna, Cusano Angela Maria, Netti Paolo.
Title	A process for providing hydrorepellent properties to a fibrous material and thereby obtained hydrophobic materials and articles.

Short Description

The system aims at detecting a single strand target nucleotide sequence and comprises:

• at least one first nucleic acid probe from 10 to 14 bases, to the 5’ end of which at least one fluorophore is bound;

• at least one second nucleic acid probe from 35 to 50 bases, comprising, from the 5’ to the 3’ end;

• a first segment having a nucleotide sequence complementary to the first nucleic acid probe;

• at least one quencher;

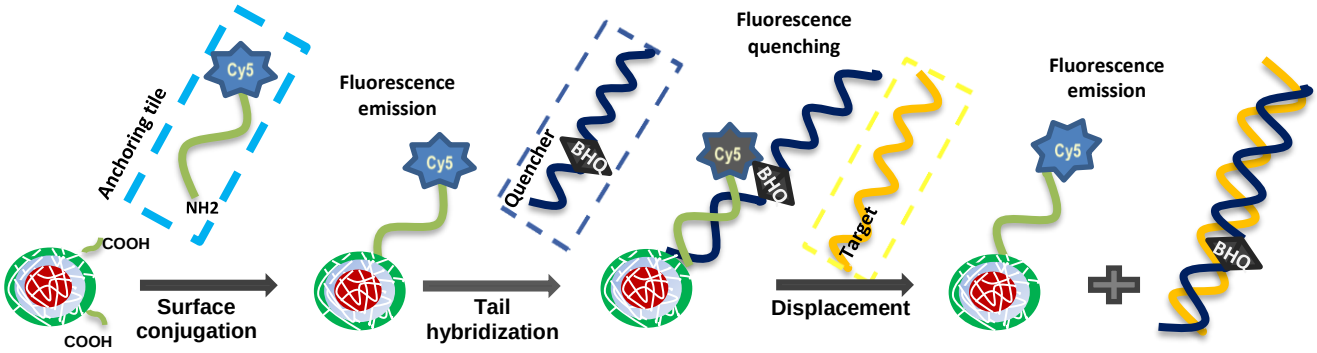
• a second segment having a nucleotide sequence complementary to at least part of the target nucleotide sequence.

IIT TECHNOLOGY

The scope of the invention is to detect and quantify the oligonucleotide (ssDNA or ssRNA) characteristic sequence of biological entities in a very low concentration, according to a multiplexed assay. Current approaches consist in real time polymerase chain reaction (RT-PCR) and blotting methods, which need several amplification steps and calibration systems during the process, or alternatively, microarrays, which need a complex procedure of fabrication of the chip.

The IIT technology features an assay platform composed by particles capable to detect, in a multiplex approach, single strand DNA molecules of different length (20-100 bases), named “ssDNA target”. The multiplex approach is guaranteed by particles provided with combinations of fluorescence barcodes. The mechanism of detection is based on double strand displacement by using linear DNA molecules directly mounted on the surface of the particles which are made up of synthetic polymer hydrogel, named microgel. Accordingly, the platform assay consists of an engineered probe mounted on encoded microgels, able to capture and reveal “the capture event” through fluorescence emission, based on double strand displacement assay. The encoded microgels are provided by a wide range of fluorescence-based codes for the multiplex assay.

As illustrated below, on the surface carboxylic acids of microgels, a single strand DNA (“ssDNA tail”), with a fluorochrome molecule on the 3’ position, is covalently immobilized through the amine on the 5’ position. This ssDNA tail is then partially hybridized with a complementary strand providing a quencher (“quencher ssDNA”), on an internal position of the molecule in order to bring in close proximity the fluorophore/quencher pair. The partial hybridization leaves a strand capable to still capture oligonucleotides (“ssDNA target”) in solution. The contact with a solution containing the “ssDNA target” brings to a displacement of the “quencher ssDNA” due to its hybridization with the “ssDNA target”. This allows the emission of the fluorochrome on DNA tail. The pair “ssDNA tail”/ “quenching ssDNA” is designed on the basis of the “ssDNA target”. The integration on a single microgel of a large number of ssDNA tails as well as the displacement mechanism capable to recover the fluorescence emission allows for the detection of the target DNA at low concentration.



As regard to the probe, the quencher ssDNA is designed to partially hybridize with the “ssDNA tail” on the microgel, leaving a single strand free to capture its specific target molecules. The “quencher ssDNA” is provided by a nucleotide base modified by a quencher in order to put it in close contact to the Cy5 on the “ssDNA tail”. Advantages of this approach are represented by the possibility of tuning the quencher-

fluorophore ratio for noise minimization, and the flexibility of modifying the lengths of the "quencher ssDNA" and the immobilized "ssDNA tail" for improving the specificity and kinetics of the assay.

The entire platform described has the following novel characteristics able to bring the invention towards the point-of-care (POC) applications:

a) multiplex ability with low costs;
b) probe design capable to detect nucleotides with high sensitivity and with a great flexibility to adapt the probe to different targets;
c) possibility to be compatible with microfluidic devices.

Microparticle based assays are increasingly used as liquid-ELISA or as alternative to the microarray technology to detect DNA. The advantages in using beads are related, mostly, to the high rate kinetic reactions (lowering the time of assay), the possibility to assemble and manipulate the particles in miniaturized devices (lab-on-a-chip) and lower costs of production. The particles can be made of different materials, shape and size.

The invention can allow the direct detection of oligonucleotides (ssDNA and ssRNA) of different length (20-100 bases) without the need of intermediate steps of amplification in a multiplex way and with a low limit detection down to $1E^{-19}$M, and an upper limit of detection up to $1E^{-11}$M. This can fit the range where the use of more complicated and expensive RT-PCR or PCR is mandatory. The proposed use is mostly related to any application where the low concentration of ssDNA is not detectable by other conventional approaches.

Proof of concept of the invention was provided by using genetic material specific for viruses such as SARS, HIV, HCV. Such application can be covered by a preliminary inverse transcriptase to convert ssRNA into ssDNA, followed by an enzymatic lyses. The identification can be addressed by targeting specific portion of the RNA sequence. The typical length of such sequences range from 20-40 bases.

In particular, this assay platform can be used to directly quantify circulating miRNA (micro RNA) that can be used as potentially biomarkers of various diseases, particularly cancer (MIRTEC Project – **MIR**na **T**echnology for **C**ancer).

The project is being submitted by IIT scientist within the Horizon 2020 framework of EU-funded projects and entails the co-operation of 12 companies/institutions from 5 European countries. The MIRTEC project aims at developing an innovative device for the detection and quantification of non-coding RNA cancer biomarkers (microRNAs or miRNAs) in complex fluids (plasma/serum) by combining innovative nano-engineered materials (micro/nanoparticles) with an advanced microfluidic chip. Some serum proteins are presently available for clinical use as biomarkers (carcinoma antigen-125, carcinoembryonic antigen, and prostate specific antigen); they are, however, also detectable in healthy individuals, albeit at lower concentrations. Molecular profiling based on DNA/RNA analysis is rapidly joining histopathological tissue examination to improve prognostic stratification and therapy selection for cancer patients. Moreover, these same tissue markers can also be found in circulation, and proper technologies can help to establish them as highly effective cancer biomarkers. Within this framework, miRNAs, 20-24 nucleotides long RNAs, have become increasingly important as biomarkers. The MIRTEC project has the objective to set up an integrated flexible chip for sensitive detection and quantification of miRNA biomarkers in complex matrices (plasma/serum/blood, biological fluids) combining an innovative detection assay based on micro-nanoparticles and an advanced microfluidic platform for sample pre-processing and analysis. It can be used for an absolute quantification of miRNAs without separation, purification and extraction. Preliminary

experiments indicate that the limit of detection for MIRTEC technology is around femto-attoMolar (10^{-15} - 10^{-18}). Other preliminary results demonstrated that MIRTEC allows detection of 3 or 4 miRNAs simultaneously, and expected multiplex ability of 10 miRNAs can be achieved.

Circulating cell-free microRNAs (cfmiRNAs) are optimal biomarkers owing to their presence and high stability in blood, urine and other body fluids. Several studies in breast, colon, and lung cancer patients showed that serum/plasma levels of specific miRNAs had shown remarkable sensitivity and specificity even in the early stage setting of the disease. The demonstration that cfmiRNA levels can distinguish cancer patients from healthy subjects has now been extended to the follow-up of patients, thus showing that cfmiRNAs represent diagnostic markers able to detect recurrences. Additionally, cfmiRNAs were shown to represent potentially powerful predictors of therapy response. The final aim of the project is, indeed, the development of a microdevice for automated and reliable quantification of cfmiRNAs without the need of extraction and amplification steps, with adequate multiplex ability along with limit of detection and dynamic range fitting the specific purpose. Novel materials functionalized at micro and nano scale according to bio-inspired approaches will be used as advanced sensors for detection of circulating miRNAs. These materials will be integrated in a microfluidic chip that pre-treats a blood sample, mixes it with sensor particles and performs multiplexed detection in fluorescence. The proof of principle of this approach will be attempted on clinically tested arrays of miRNAs for cancer diagnosis. Preliminary results show that MIRTEC can be used for absolute quantification directly in serum.

In principle, such ssDNA can be detected in any substance, food, paintings, chemicals and adhesives, as well as various tissues and toxins obtained after industrial processes at cold and warm temperature.

The development of rapid detection strategies toward POC applications has been receiving increasing attention due to the time and labour-intensive protocols associated with traditional assays. In particular, assays that are free of separation, amplification, and other related operations are highly desirable. These assays could dramatically simplify the assay protocol and facilitate rapid diagnostics in resource-limited settings.

MARKET ANALYSIS

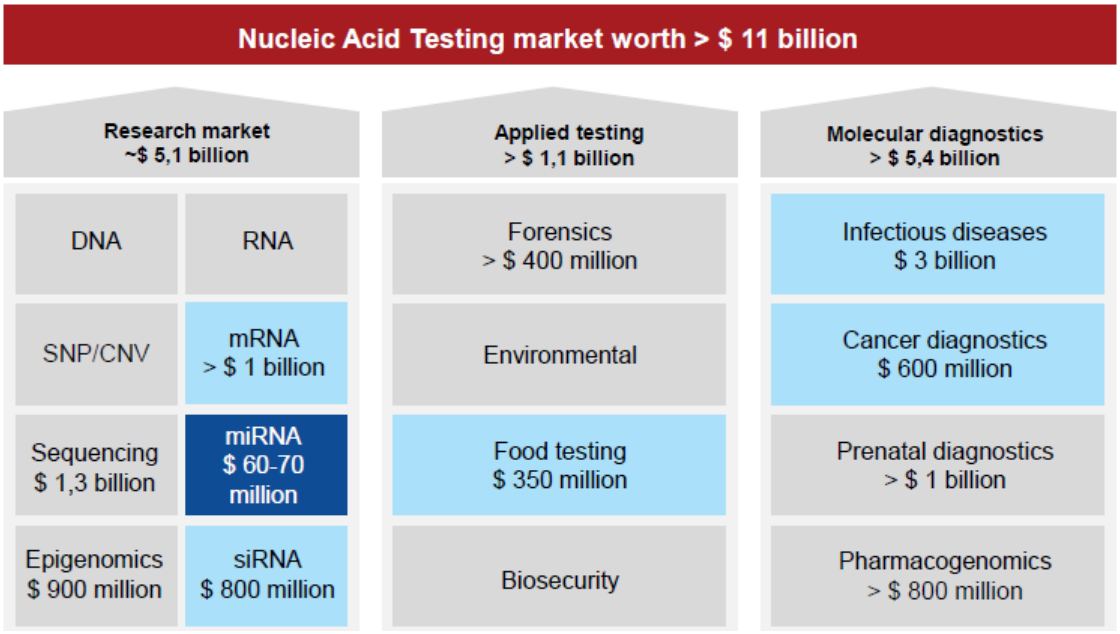
Based on the technology described in WO 2014/102748 A1, IIT internal documentation (Horizon 2020 Project) on the technology and related literature publications by the inventors and competitors, the Nucleic Acid Testing market (a subset of the In Vitro Diagnostic - IVD - market) has been analyzed through a web search-based retrieval of free-of-charge specific information along with the specific miRNA (microRNA) market sub-segment.

Nucleic Acid Testing (NAT) Market

Most of nucleic acid tests are performed in order to detect the presence of viral DNAs or RNAs in blood samples of patients. The three major processes involved in NAT are sample pooling and nucleic acid (NA) extraction, target NA amplification and target amplicon NA detection. Major NAT technologies include polymerase chain reaction (PCR), strand displacement amplification (SDA), ligase chain reaction (LCR), transcription-mediated amplification (TMA), and nucleic acid sequence based amplification (NASBA). Based on its major applications, NAT market can be classified into five major segments namely infectious diseases, genetic diseases, cancer, forensic testing and paternity testing.

Major growth drivers for the NAT market include increasing prevalence of infectious diseases, cancer and genetic diseases, growing demand for technological advancements in testing methods, increasing end user acceptance and favorable regulatory mechanisms worldwide. It was estimated that approximately one billion people suffered from various infectious diseases worldwide in 2012, which is one of the major segments of the NAT market, thus will affect this markets growth in future. Growing demand for new and improved testing methods that utilizes new reagent systems and automated amplification systems in a wide range of applications will also provide this market a larger share in the coming future.

Internal data elaborated in 2013 from one of the most active companies in this field, Exiqon, were presented in February 2013 and describe a very optimistic scenario, with the NAT market worth ≥ USD 11 billion, in turn sub-divided in Research market (USD 5.1 billion), Applied testing market (USD 1.1 billion) and Molecular Diagnostic market (USD 5.4 billion, see below). Growing demand for nucleic acid testing in developing customized medicines and in the enhancing healthcare sector within the life sciences industry is expected to accelerate the market in the coming years.



Slide adapted from Exiqon company presentation "Annual Report 2012" (Feb. 2013)

Geographically, North America dominated the global NAT market with the largest share in terms of revenue, followed by Europe. Asia-Pacific is expected to be the fastest growing market in the coming future because in most of its countries, the NAT market is currently at nascent stage or underpenetrated. This region is likely to evolve under the influence of increasing awareness regarding the testing methods and continuously improving economic condition.

NAT is one of the fastest-growing segments of the molecular diagnostics market; it outweighs the traditional culture techniques in terms of sensitivity and speed. NAT based tools are widely being used for developing in-vitro diagnostics (IVD) and for discovery and manufacture of novel biomarkers. NAT is the most advanced diagnostic test for examining pathogens of interest and other various genetic disorders. Despite NAT being in the developing stages, the tests are one of the fastest growing segments of the IVD industry. The segment is mainly driven by viral load applications, HIV, hepatitis and CMV diagnostics. Adoption of the nucleic acid testing by the clinical laboratory field has been at a rather slow pace than estimated. However, the adoption rate of molecular diagnostics is most likely to increase in the coming years, thanks to the advent of various new technologies such as blotting technologies, amplification technologies, microarray, RNA inhibition analysis, probe technologies, electrophoretic technologies and others.

In another report issued by Markets and Markets, titled *"Nucleic Acid Isolation and Purification Market by Technology (Column based, Reagent based, Magnetic bead based), Consumables & Instruments, Application (Plasmid DNA isolation, MIRNA isolation, Total RNA isolation), and End Users - Global Forecast to 2018"*, the slightly different sub-segment market of isolation and purification technologies is expected to grow globally at a CAGR of close to 8.11% between 2013 and 2018**,** to reach USD 3.1 billion by 2018. This technology segment is further divided into column-based, magnetic bead-based, reagent-based, and other (glass fiber and anion exchange) technologies for DNA and RNA isolation and purification. Magnetic-bead

technology for DNA isolation is the fastest-growing segment in the nucleic acid isolation and purification technology market. The application segment is further divided into blood DNA isolation and purification, genomic DNA isolation and purification, microRNA isolation and purification, mRNA isolation and purification, plasmid DNA isolation and purification, total RNA isolation and purification, and PCR cleanup. MicroRNA isolation and purification is expected to grow at the highest CAGR during the forecast period. On the basis of products, this market is classified into instruments and consumables/reagents. Consumables dominated the market in 2013; however, the instruments sub-segment is expected to grow in the coming future owing to increased applications in hospitals and diagnostics.

The end-users market is segmented into academic research, hospitals and diagnostic centers, pharmaceutical and biotech companies, contract research organizations and others (forensic and food testing laboratories). Academic research accounted for the largest share in this market. However, the hospitals and diagnostic centers segment is expected to grow in the near future owing to the increased applications of nucleic acid testing in molecular diagnostics. The technological advancements and the increased government support in the form of funding are the factors that drive the nucleic acid isolation and purification market across the globe. However, decrease in R&D spending may hinder the growth of this market. The increasing applications of nucleic acid test in molecular diagnostics and point of care (POC) devices represent a huge growth opportunity for this market.

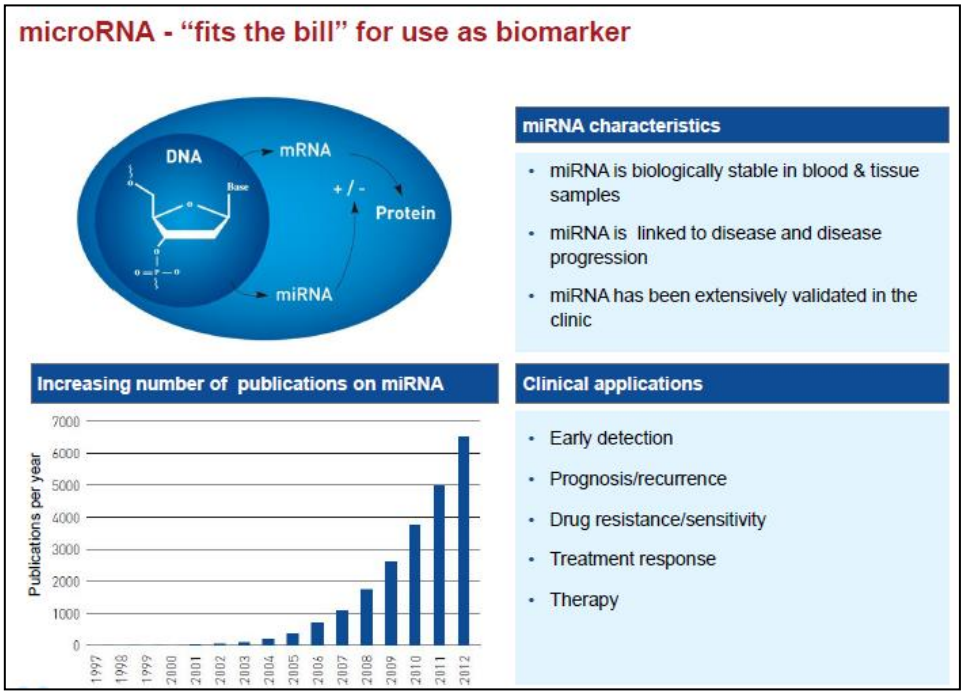
MicroRNAs (miRNAs) Market

Mature microRNAs (miRNAs) are a class of naturally occurring, small non-coding RNA molecules, about 20–24 nucleotides in length. MiRNAs have become increasingly important as biomarkers. In particular, all types of cancer are associated with the deregulation of several miRNAs, and hundreds of scientific reports have provided strong evidences that circulating miRNAs are involved in cancer evolution. Thus, the extensive information on miRNAs represents a precious tool for developing novel strategies for more efficient cancer detection, monitoring and therapy. Just in 2014, a few circulating miRNAs were identified in large groups of patients for the detection and monitoring of lung, colon and breast cancer patients.

MicroRNAs are partially complementary to one or more messenger RNA (mRNA) molecules, and their main function is to downregulate gene expression in a variety of manners, including translational repression, mRNA cleavage, and deadenylation. They were first described in 1993 by Lee and colleagues, and the term microRNA was coined in 2001. Thousands of miRNAs have since been identified in various organisms through random cloning and sequencing or computational prediction.

Although the first miRNA was identified over ten years ago, it is only recently that researchers have begun to understand the scope and diversity of these regulatory molecules. Growing evidence shows that miRNAs exhibit a variety of crucial regulatory functions related to cell growth, development, and differentiation, and are associated with a wide variety of human diseases. Several miRNAs have been linked to cancer and heart disease. Expression analysis studies reveal perturbed miRNA expression in tumors compared to normal tissues. MicroRNAs are deregulated in breast, lung, and colon cancer, and upregulated in Burkitt's and other human B-cell lymphomas**.** As a consequence, human miRNAs are likely to be highly useful as biomarkers, especially for future cancer diagnostics, and are rapidly emerging as attractive targets for disease intervention.

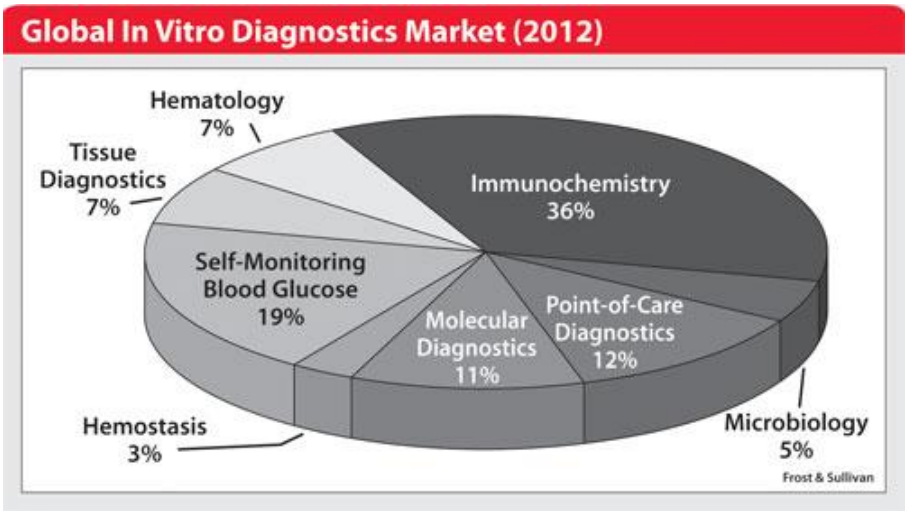
Most of these things are well summarized by a slide taken from Exiqon company presentation "Annual Report 2012" (Feb. 2013, see below).



Slide adapted from Exiqon company presentation "Annual Report 2012" (Feb. 2013)

In addition to their link with cancer, microRNAs play an important role in the control of diverse aspects of cardiac function and dysfunction as well. Including myocyte growth, integrity of the ventricular wall, contractility, gene expression, and maintenance of cardiac rhythm. The mis-expression of miRNAs has been shown to be necessary and sufficient for multiple forms of heart disease.

From the market standpoint, the MiRNA technology falls within the molecular diagnostic device and POC device categories, which are part of the much bigger In vitro Diagnostic (IVD) market.

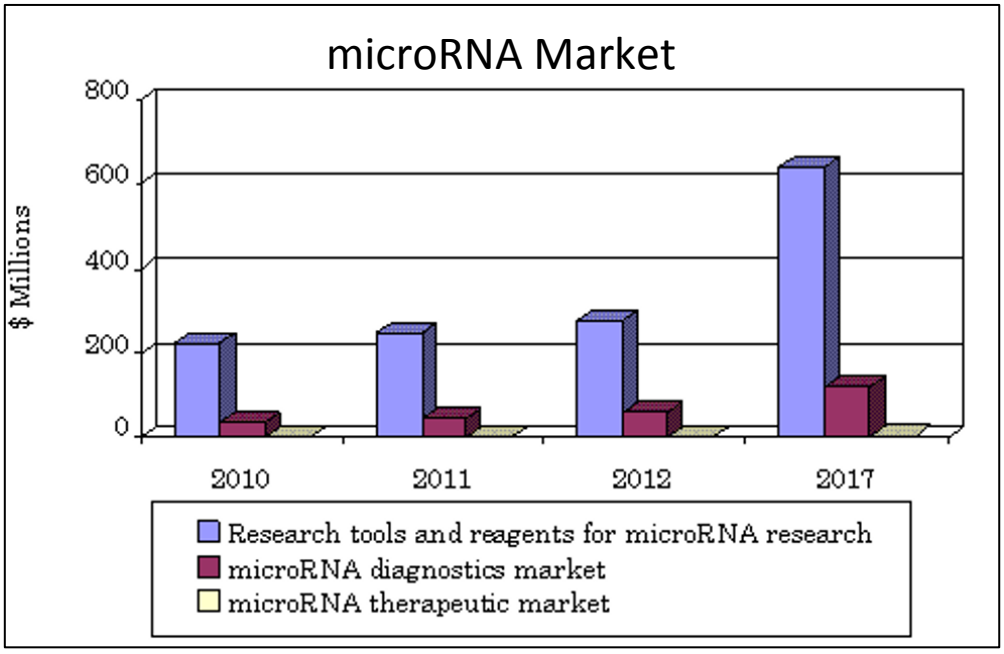


Although the Immunochemistry sub-segment is the driving force of the IVD market accounting for 36% of global sales, molecular diagnostic device and POC device topped 11% and 12% in 2012 respectively (see

previous figure, data adapted from Frost & Sullivan) and are expected to grow at a fast pace doubling the sales every two years.

According to a new technical market research report, *"MicroRNA Diagnostics and Therapeutics: Technologies and Global Markets"*, issued in November 2012 from BCC Research, the global microRNA research tools market was valued at nearly USD 295.1 million in 2011 and should reach nearly USD 338.3 million in 2012. Total market value is expected to reach USD 763 million in 2017 after increasing at a five-year compounded annual growth rate (CAGR) of 17.7%.

The market for microRNA can be broken down into three segments: research tools and reagents for microRNA research, the microRNA diagnostics market, and the microRNA therapeutic market. The segment made up of tools and reagents for microRNA research was valued at USD 278 million in 2012, and is expected to reach USD 640 million in 2017, with a CAGR of 18.1%. As a segment, the microRNA diagnostic segment was valued at USD 60 million in 2012, and is expected to reach USD 120 million in 2017, with a CAGR of 14.9%. The microRNA therapeutics market was USD 0.3 million in 2012, and is expected to reach USD 3 million in 2017, with a CAGR of 60.7%.



COMPETITIVE SCENARIO

Leading Companies in the Nucleic Acid Testing (NAT) Market

The Nucleic Acid Testing (NAT) is currently underpenetrated and in its nascent stage of development; as a consequence, it appears very fragmented. Below a list of some key players in the market:

- Abbott Molecular Inc. (USA, http://www.abbottmolecular.com/us/home.html)
- Agensys Inc. (USA, http://www.agensys.com/)
- Agilent Technologies Inc. (USA, http://www.genomics.agilent.com)
- Applied Biosystems Group (USA, http://www.appliedbiosystems.com/absite/us/en/home.html)
- Beckman Coulter Inc. (USA, https://www.beckmancoulter.com)
- Becton Dickinson and Company (USA, http://www.bd.com/)
- bioMérieux SA (France, http://www.biomerieux.com/),
- Bio-Rad Laboratories Inc. (USA, http://www.bio-rad.com)
- Clonit Srl (Italy, http://www.clonit.it/en-GB/molecular-biology-in-diagnostic/)
- Clontech Laboratories Inc. (USA, http://www.clontech.com)
- Corixa Inc. (USA, http://www.coulterpharm.com/)
- Danaher Corporation (USA, http://www.danaher.com/)
- Epicentre Technologies (USA, http://www.epibio.com/)
- FMC Corporation (USA, http://www.fmc.com/)
- F. Hoffmann-La Roche Ltd. (USA, http://www.roche.com/index.htm)
- GE Healthcare Lifesciences (UK, http://www.gelifesciences.com)
- Genomic Health Inc. (USA, http://www.genomichealth.com/)
- Gen-Probe Inc. (USA, http://www.gen-probe.com/)
- Genzyme Corporation (USA, http://www.genzyme.com/)
- Hologic (USA, http://www.hologic.com/en/)
- IBA GmbH (Germany, https://www.iba-lifesciences.com/home.html)
- IDEXX Laboratories Inc. (USA, https://www.idexx.com/corporate/home.html)
- Illumina Inc. (USA, http://www.illumina.com/)
- Life Technologies Corp. (USA, http://www.lifetechnologies.com/it/en/home.html)
- Kamiya Biomedical Co. (USA, http://www.kamiyabiomedical.com/)
- Mologic Ltd. (UK, http://mologic.co.uk/)
- Myriad Genetics Inc. (USA, https://www.myriad.com/)
- Novartis AG (Switzerland, http://www.novartis.com/)
- Oncor Inc. (USA, http://www.oncor.com/EN/Pages/default.aspx)
- Promega Corporation (Italy, http://ita.promega.com/)
- Qiagen N.V. (Netherlands, http://www.qiagen.com/)
- Sekisui Diagnostics (USA, http://www.sekisuidiagnostics.com/)
- Sequenom Inc. (USA, http://www.sequenom.com/)

- Siemens Healthcare Diagnostics (Germany, http://www.healthcare.siemens.com/laboratory-diagnostics)
- Sigma-Aldrich Co. Llc (USA, http://www.sigmaaldrich.com/italy.html)
- Signet Laboratories Inc. (USA, http://www.covance.com/)
- Tecan Group Ltd. (Switzerland, http://www.tecan.com)
- Thermo Fischer Scientific Inc. (USA, http://www.thermofisher.com/en/home.html)

Leading Companies in the MicroRNAs (miRNAs) Market

A growing number of pharmaceutical and biotech companies are becoming involved in miRNA research due to advancements in molecular diagnostics and therapeutics, thereby, expanding and embracing cardiovascular, virology, endocrinology, plant science and genetic disease fields. However, high investment cost, stringent regulations and lack of skilled professionals obstruct the growth of global microRNA market. Increasing mergers and collaborations between biotech companies and government research organizations seem the key trends for the global microRNA market. Below a list of the major players:

- Alnylam Pharmaceuticals Inc. (USA, http://www.alnylam.com/)
- Exiqon A/S (Denmark, http://www.exiqon.com/)
- Santaris Pharma A/S (Denmark, http://www.santaris.com/)
- Access Pharmaceuticals (USA, http://www.accesspharma.com/)
- Aegera Therapeutics Inc. (Canada, http://www.aegera.com/)
- Affymetrix Inc. (USA, http://www.affymetrix.com)
- Agilent Technologies Inc. (USA, http://www.genomics.agilent.com)
- Isarna Therapeutics (Germany, http://www.isarna-therapeutics.com/)
- Aparna Biosciences Corp. (USA, http://www.aparnabio.com/)
- Applied Biological Materials Inc. (Canada, http://www.abmgood.com/)
- Arrowhead Research Corp. (USA, http://www.arrowheadresearch.com/)
- AstraZeneca Pharmaceuticals LP (UK, http://www.astrazeneca-us.com/home/)
- Asuragen Inc. (USA, http://asuragen.com/)
- Benitec Biopharma Ltd. (USA, http://www.benitec.com/)
- BioCancell Therapeutics Inc. (USA, http://www.biocancell.com/)
- Biogen Idec Inc. (USA, http://www.biogenidec.com/)
- CBC Comprehensive Biomarker Center GmbH (Germany, http://www.cbioc.com/en/)
- Clontech Laboratories Inc. (USA, http://www.clontech.com/)
- Dicerna Pharmaceuticals Inc. (USA, http://www.dicerna.com/)
- Eli Lilly and Co. (USA, http://www.lilly.com)
- Expression Genetics Inc. (USA, http://www.egeninc.com/)
- Hoffmann-La Roche Ltd. (Switzerland, http://www.roche.com/index.htm)
- Fluidigm Corp. (USA, http://www.fluidigm.com/)
- GE Healthcare (UK, http://dharmacon.gelifesciences.com/dharmacon/)

- GeneCopoeia Inc. (USA, http://www.genecopoeia.com/)
- GenoSensor Corp. (USA, http://www.genosensorcorp.com/)
- Gensignia Inc. (USA, http://www.gensignia.com/)
- Groove Biopharma (USA, http://www.groovebiopharma.com/)
- GlaxoSmithKline Plc (UK, http://www.gsk.com/)
- HTG Molecular Diagnostics Inc. (USA, http://www.htgmolecular.com/)
- Idera Pharmaceuticals Inc. (USA, http://www.iderapharma.com/)
- Illumina Inc. (USA, http://www.illumina.com/)
- InteRNA Technologies B.V. (Netherlands, http://www.interna-technologies.com/)
- Isis Pharmaceuticals Inc. (USA, http://www.isispharm.com/index.htm)
- LC Sciences Llc (USA, http://www.lcsciences.com/)
- Life Technologies Corp. (USA, http://www.lifetechnologies.com/it/en/home.html)
- Merck & Co. Inc. (USA, http://www.merck.com/index.html)
- miRagen Therapeutics Inc. (USA, http://miragentherapeutics.com/)
- Mirna Therapeutics Inc. (USA, http://www.mirnatherapeutics.com/)
- NanoString Technologies Inc. (USA, http://www.nanostring.com/)
- Norgen Biotek Corp. (Canada, https://norgenbiotek.com/)
- Novartis AG (Switzerland, http://www.novartis.com/)
- Pfizer Inc. (USA, http://www.pfizer.com/)
- Phalanx Biotech Group (Taiwan, http://www.phalanxbiotech.com/main.php)
- PhaseRx Inc. (USA, http://www.phaserx.com/)
- Prolias Technologies Inc. (USA, http://www.proliastechnologies.com/)
- Qiagen N.V. (Netherlands, http://www.qiagen.com/)
- Quanta Biosciences (USA, http://www.quantabio.com/)
- Quark Pharmaceuticals Inc. (USA, http://www.quarkpharma.com/)
- Regulus Therapeutics Inc. (USA, http://www.regulusrx.com/)
- Sanofi US (USA, http://www.sanofi.us)
- Sarepta Therapeutics (USA, http://www.sarepta.com/)
- Sigma-Aldrich Co. Llc (USA, http://www.sigmaaldrich.com/united-states.html)
- Silence Therapeutics Plc (UK, http://silence-therapeutics.com/)
- Sirnaomics Inc. (USA, http://www.sirnaomics.com/
- siRNAsense AS (Norway, http://www.sirnasense.com/),
- Sylentis SA (Spain, http://www.sylentis.com/)
- Tacere Therapeutics Inc. (USA, http://www.tacerebio.com/)
- Theradiag SA (France, http://www.theradiag.com/en/)
- Thermo Fisher Scientific Inc. (USA, http://www.thermofisher.com/en/home.html)
- WaferGen Biosystems Inc. (USA, http://www.wafergen.com/)

CONTACTS @IIT

Fondazione Istituto Italiano di Tecnologia (IIT)
Via Morego 30 - 16163 Genova, Italy
Tel: +39 010 71781 - Fax: +39 010 720321
C.F. 97329350587 - P.I. 09198791007
Technology Transfer – technology.transfer@iit.it