FONDAZIONE ISTITUTO ITALIANO DI TECNOLOGIA

A TECHNOLOGY TEASER

NANODIAGNOSTIC COLORIMETRIC TESTS

ISTITUTO ITALIANO DI TECNOLOGIA

Released on January 2017

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

Nowadays in vitro diagnostics have to face new technological challenges which existing solutions can hardly address. Traditional in vitro diagnostics generally employ costly instrumentation and reagents and require specialized laboratories, trained personnel and lengthy procedures. These requirements are hampering a larger and broader application of diagnostic tests, such as the large-scale implementation of population screenings, environmental monitoring and food quality control. In order to better address these types of applications, a new approach is necessary and new tests are needed: cost-effectiveness, fastness and simplicity are expected to be suitable drivers for the future diagnostics.

The applications for a new kind of diagnostics are numerous and still to fully understand. For instance, there is a raising demand for food safety and quality control. Food supply chain has many players and is becoming more and more competitive: the risk of contamination along the chain (by voluntary counterfeiting and/or by pathogens) is high enough to justify the investment in new technologies, which are compatible in term of time and cost with existing production and supply processes. Under the pressure of the consumers, food companies and food associations are becoming aware of the problem and are looking for new solutions, because traditional technologies fail to meet the new needs.
More applications are expected in the environmental monitoring and in healthcare market: preventive screenings and ultra-early diagnoses of pathologies, but also the definition of personalized therapies are just few examples.

IIT solution for nanodiagnostic tests has to be inserted in this framework. These tests are already proving their validity with food products. Moreover, the technology is so versatile that can be used in a range of very different applications, even outside food industry. IIT nanodiagnostic colorimetric tests can represent an enabling technology, a new platform for a different approach to diagnostics.

These technologies represent a unique chance for companies interested, or willing to branch out, in food safety testing and fraud prevention markets as well as in the in vitro diagnostic market and the molecular biology reagents market. 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.

INTELLECTUAL PROPERTY

PCT International Application #	PCT/IB2015/059546 - 11 December 2015
Priority Application #	IT 102014902316740 (TO2014A001037) - 15 December 2014
Applicant	Fondazione Istituto Italiano di Tecnologia
Inventors	Pier Paolo POMPA, Paola VALENTINI
Title	A Method For The Colorimetric Detection Of The Amplification Of A Target Nucleic Acid Sequence

Short Description

The invention relates to a system for the detection of Polymerase Chain Reaction (PCR) products which is based on gold nanoparticles (AuNP) functionalized with DNA oligonucleotides. Unlike currently used technologies, the invention does not require instrumentations, nor processing steps, being, on the contrary, a rapid one-step assay only requiring the addition of pre-mixed reagents to the PCR reaction products, which returns a visual readout in few minutes. This rapid test will have relevance in molecular biology applications both in scientific research and in clinical laboratories and it will be particularly useful in those situations where simplifying large scale genetic screening (for instance, for searching infectious diseases nucleic acids) may be relevant.

PCT International Application #	PCT/IB2015/059541 - 11 December 2015
Priority Application #	IT 102014902316743 (TO2014A001040) - 15 December 2014
Applicant	Fondazione Istituto Italiano di Tecnologia
Inventors	Pier Paolo POMPA, Paola VALENTINI, Paola CECERE
Title	Method For The Colorimetric Detection Of Contamination With Nucleases

Short Description

The invention relates to a nanoparticle-based system for the detection of nuclease contaminations, which reaches sensitivity and specificity equal or superior to those of currently used technologies but, unlike the latter, does not require instrumentations, nor processing steps, being, on the contrary, a two-step assay only requiring the mixing of the components and naked-eye inspection. This rapid test will have relevance as routine control in molecular biology applications in scientific research, but it might also find other commercial applications in the field of quality controls in clinical laboratories and production facilities of reagents for molecular biology.

IIT TECHNOLOGY

The understanding of IIT solutions is based on two well-known facts: the properties of colloidal gold nanoparticles and the polymerase chain reaction (PCR). Before the description of the solution, a short overview of both of them is reported.

Colloidal gold nanoparticles

Colloidal gold is a suspension of gold nanoparticles in a fluid, usually water. The colorimetric properties of colloidal gold are well-known: according to the distance of the particles, the solution looks differently.
When the particles are aggregated, the solution looks purple/bluish, while when the particles are scattered, the solution looks red. For similar reasons, also the size of the particles can affect the color of the solution (Fig.1).

Figure 1. Colloidal gold solutions containing nanoparticles which have different sizes.

Thanks to this property, colloidal gold nanoparticles have applications in a wide variety of areas, including electron microscopy, electronics, nanotechnology and materials science.

Polymerase Chain Reaction (PCR)

The polymerase chain reaction (PCR) is a process for the amplification of DNA material. It is a common technique, which can be used in several procedures, for instance in the diagnosis of hereditary diseases, in the identification of genetic fingerprinting and the in DNA cloning for sequencing.

The process is divided in repeated thermal cycles (about 20-40 repetitions); each cycles has three main phases:

1) **Denaturation**. The temperature is increased in order to break the bonds between complementary bases; this step leads to single-stranded DNA molecules.
2) **Annealing**. The temperature is lowered so that a set of specific bases (so-called “primers”) can bind with the free extremities of the single-stranded DNA molecules. The bases contained in the primers have to be complementary to the free DNA molecules, in order to bind.

3) **Extension**. Starting from the primers, a DNA polymerase elongates the DNA strand using some reagents available in the solution for the creation of the complementary bases.

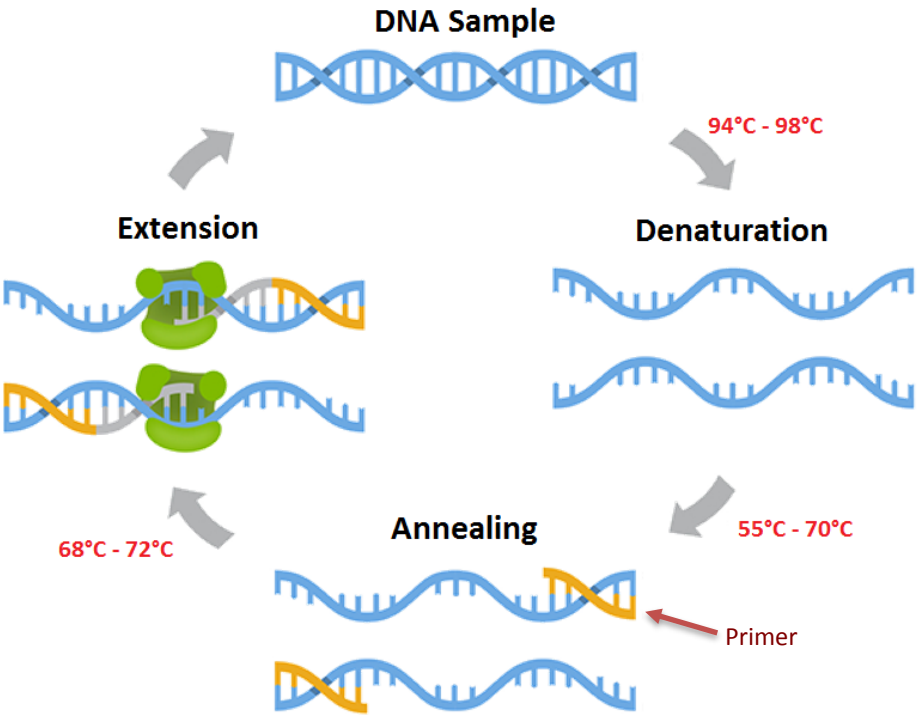

Figure 2. A cycle of PCR. Every cycle amplifies the quantity of the target DNA.

The process can be repeated several times, until there are no more reagents available. Too many cycles can lead to undesired side effects, such as the amplification of contaminants.

IIT solutions

IIT solutions involve the utilization of functionalized gold nanoparticles for the detection of target nucleic acids. If the target is detected, the solution changes color. The two patents refer to slightly different technologies for very different applications.

Detection of the amplification of a target nucleic acid sequence (PCT/IB2015/059546)

This technology aims to understand if a certain solution contains a specific DNA target. The entire test requires about two hours and is extremely sensitive, since very low quantities of the target can be efficiently detected.

This is possible through an asymmetric PCR, so-called “asymmetric PCR”, because an asymmetric distribution of the reagents in the solution is involved in order to obtain a single stranded amplicon. The scheme of the process is reported in the picture below (Fig.3). One of the two primers has an additional short sequence at one of its end. During the reactions, the complementary strand of this free extremity is recreated by DNA polymerase. This new segment is called universal tag sequence (TAG) and it will provide the evidence of the presence of the target in the solution. The whole process triggers only if the target is present in the solution.

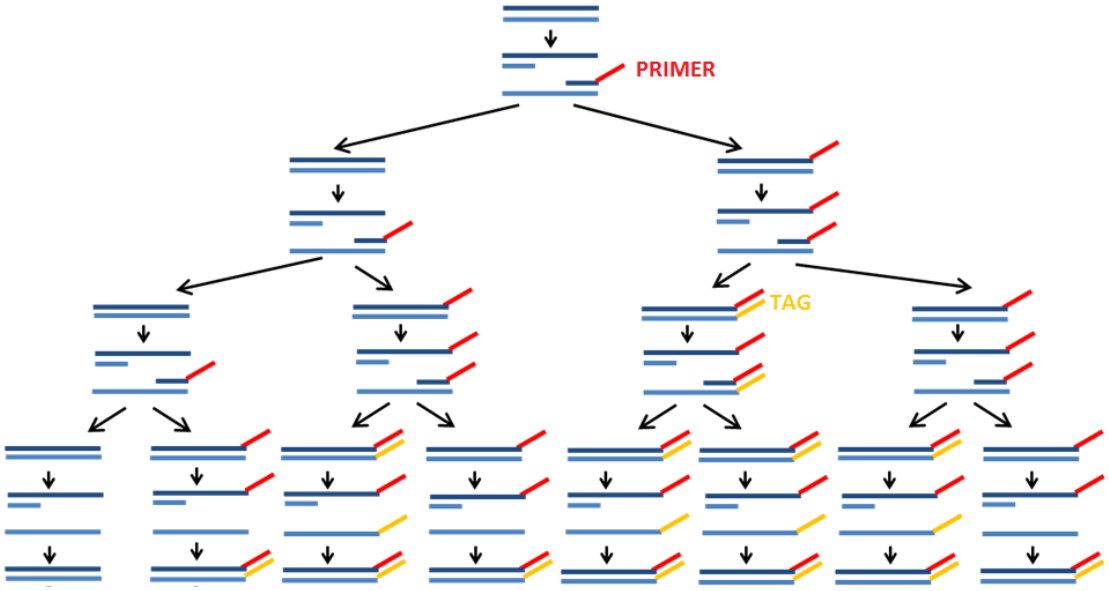

Figure 3. Asymmetric PCR scheme.

If the target is present, the output of the PCR is a solution in which a great quantity of TAGs is present.
A small amount of the output is inserted in a colloidal solution of gold nanoparticles (AuNP). The gold nanoparticles are functionalized with two sets oligonucleotides which are complementary to two different portions of the TAG.

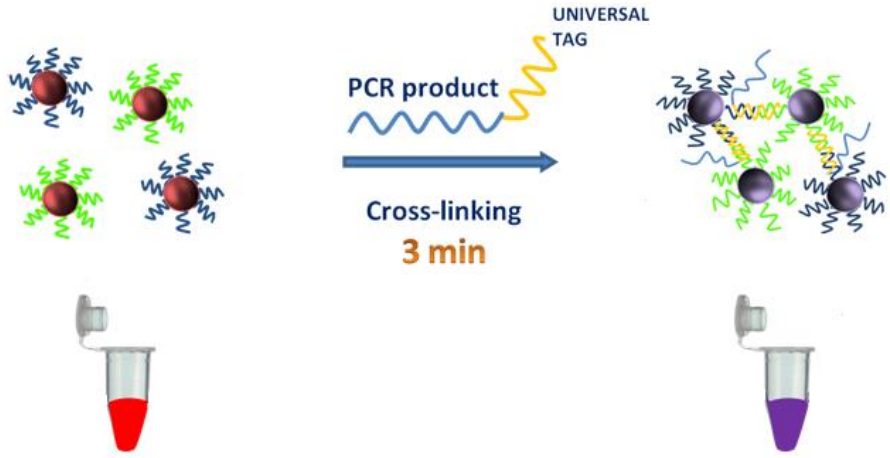

Figure 4. The PCR product works as a nucleotide linker when the tag is present.

The TAGs bind to the two kinds of gold nanoparticles, which create a reticulum, while getting nearer. As a consequence, the solution changes color, moving from red to purple (Fig.4). On the contrary, if there is no TAGs, because the PCR didn't amplify the target, the solution doesn't change color.
The priority application covers also some variations of this process: changing the functionalization of the nanoparticles and using TAGs of different length, it is possible to use this test for symmetrical PCR.

The primary application of this technology is the creation of low-cost, almost on field and frequent tests for the detection of a target DNA material in a sample. The test consists of three main steps, as shown in the picture below (Fig.5):

Figure 5. The three steps which composes the test.

Since the test is highly sensitive the DNA samples can be "dirty", the DNA extraction can be performed from raw matrices; the amplification requires a standard PCR; the detection is colorimetric and instrument-free. Besides, the test is very robust and universal: only a minor customization is necessary to adapt it to different matrices and targets.

Detection of the contamination with nucleases (PCT/IB2015/059541)

Nucleases are enzymes capable of cleaving the nucleotides which compose a nucleic acid. Nucleases can be divided in two main groups: endonucleases and exonucleases. Endonucleases break nucleic acid chains in the interior, rather than at the ends of the molecule; a nuclease that functions by removing nucleotides from the ends of the molecule is called an exonuclease.
Deoxyribonuclease (DNase) and Ribonuclease (RNase) are nucleases which catalyze the degradation of DNA and RNA, respectively (Fig. 6).

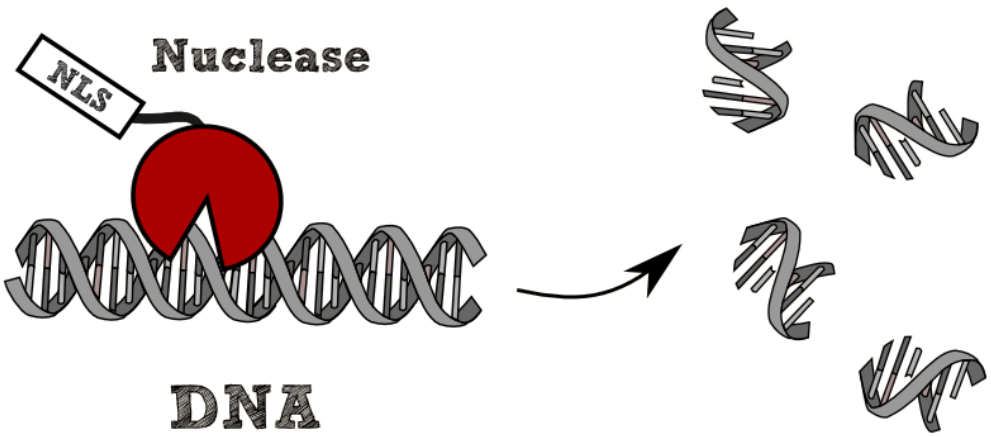

Figure 6. DNAse degrades DNA, leaving fragments of nucleic acids.

Although nucleases have several useful applications, for instance the possibility to cut DNA at specific sites, they generally represent an issue in laboratories of molecular biology: their presence can adulterate the results of the analyses.

For this reason, in these laboratories it is necessary to sterilize devices and tools and some procedures have to be respected in order to inhibit, or at least decrease, the activity of the nucleases. The presence of nucleases is periodically checked through commercial tests whose performances and usage are not optimal.
IIT technology is capable to detect nucleases in a liquid solution with very high sensitivity and a colorimetric read-out, thanks to the optical properties of the functionalized gold nanoparticles.
The test is composed of two steps, starting from the solution to be tested:

1) Addition of oligonucleotide linkers
2) Addition of the functionalized gold nanoparticles

The process is represented in the picture below (Fig.7). There are several types of linkers (A-F) which represent the most common substrates for nucleases. After the addition of the oligonucleotide linkers, it is necessary to wait for about an hour: this time is enough to get a test far more sensitive than other commercial solutions.

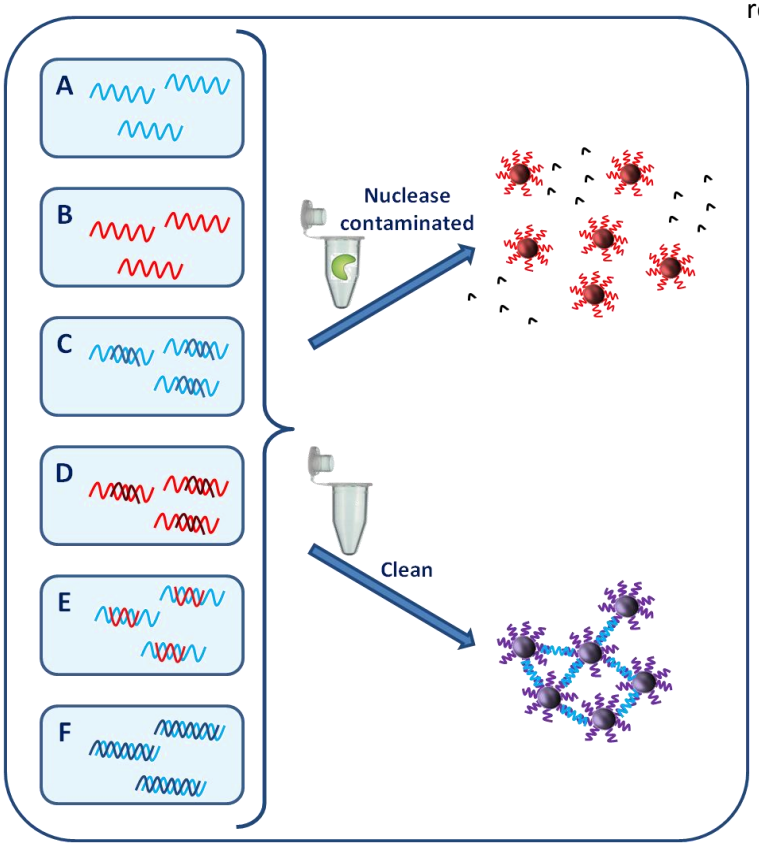

Figure 7. The linkers (A-F) are degraded by nucleases, if present.

The golden nanoparticles are functionalized with two set of oligonucleotides which are complementary to two sections of the linker.
If there are nucleases in the sample, the nucleases degrade the linkers and the result is a red solution which contains the degraded linkers and scattered golden nanoparticles; on the contrary, if there are not nucleases in the sample, the linkers are not degraded and they can bind to the complementary bases of the functionalized golden nanoparticles. This reaction leads to the reticulation of the nanoparticles which triggers a change of the color from red to purple.

The test is cost-effective and rapid. Besides, it doesn't require specific technical instrumentations.

MARKET ANALYSIS

The technology hereby described is expected to have applications in several markets.

The detection of the amplification of a target nucleic acid sequence is already a necessary and frequent activity in many laboratories. However, IIT solution opens new possibilities, thanks to the advantages which are offered: these tests are time-saving, cost-effective and can be performed almost on-field by not highly specialized operators. Two important and rising markets for these tests can be the **food safety testing** and the **food fraud prevention**.

The solution for the detection of the contamination with nucleases is suitable for the market of **molecular biology reagents**.

Food Safety Market

Consumers are becoming increasingly aware of food safety issues and are demanding increased transparency from companies; at the same time, the regulatory frameworks of developed countries are supporting these needs with more and more strict new regulations. Food companies are required to prove the safety of their products now more than ever.
Safety represents a necessary cost for food companies; sometimes, despite the effort, it can be still difficult to guarantee the safety of the product for several reasons, for instance:

- Tests are time-consuming. If the product is perishable, the required time may not be compatible with its shelf life.
- Tests are expensive. This can represent an issue for small and medium enterprises.
- Tests require specialized staff.
- Tests require instrumentation.

Moreover, food moves along the supply chain and undergo processing, cooking, transportations and other operations; every step of the supply chain is an opportunity for a contamination. IIT solution allows to overcome these issues and represents a concrete support for the consumers.
According to the report "*Food safety testing Market (traditional and rapid) by Technology, (pathogens, toxins, GMOs, pesticides and others) by contaminant, (meat & poultry, dairy, process food, fruit & vegetables and others) by Application - Global Industry Perspective, Comprehensive Analysis and Forecast, 2015 – 2021*" , the global demand for food safety testing market was valued at USD 4.8 billion in 2015, is expected to reach USD 8.04 billion in 2021 and is anticipated to grow at a CAGR of 7.8% between 2016 and 2021 (Fig.8). Nowadays, different technologies are used for testing food safety, including traditional technologies and rapid technologies. Due to some limitations of traditional food safety methods, rapid food testing technology accounted for a significant share of 2015 market. The pathogen contaminant is a leading segment in food safety market. Furthermore, GMO testing segment is expected to be the fastest growing segment over the forecast period.

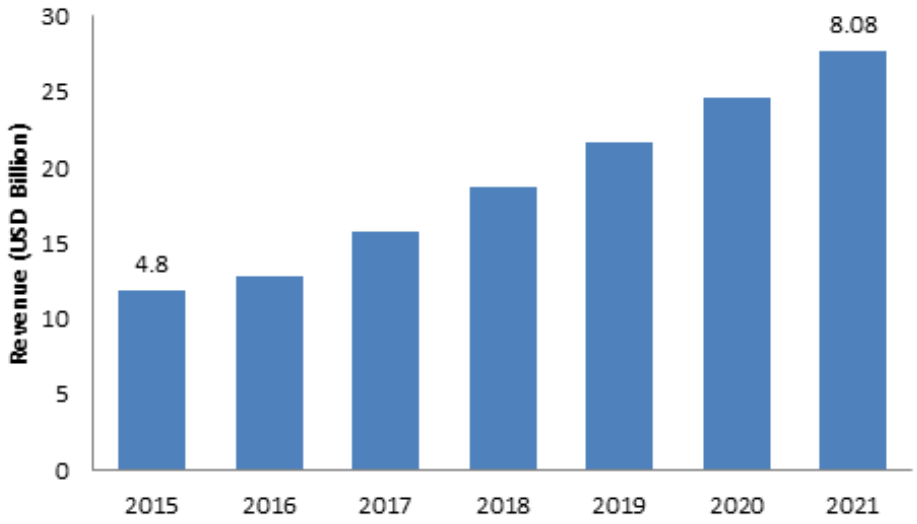

Figure 8. Food safety testing market revenues (2015-2021). Source: Zion Research Analysis 2016

A report by Markets & Markets estimates a larger market, but a similar grow rate. According to their report "*Food Safety Testing Market by Contaminant (Pathogens, Pesticides, GMOs, and Toxins), Food Tested (Meat & Poultry, Dairy Product, Processed Food, and Fruits & Vegetables), Technology (Traditional and Rapid), and by Region - Global Forecast to 2021*", the food safety testing market is projected to reach a value of USD 17.16 Billion by 2021, at a CAGR of 7.4% from 2016. The market is driven by factors such as global increase in outbreaks of foodborne illnesses and implementation of stringent food safety regulations. The high growth potential in emerging markets and untapped regions provide new opportunities for market players.

All the sources agree that pathogens represent the majority of this market, with salmonella as the first pathogen to be searched by far. According to Food Safety Magazine (Comparison of Microbiology Testing Practices, July 2013), pathogen samples are collected all along the supply chain but with different testing philosophies across the countries (Fig.9): in Asia samples are generally collected from raw materials, while the rest of the world tends to test in-process or directly the end product.

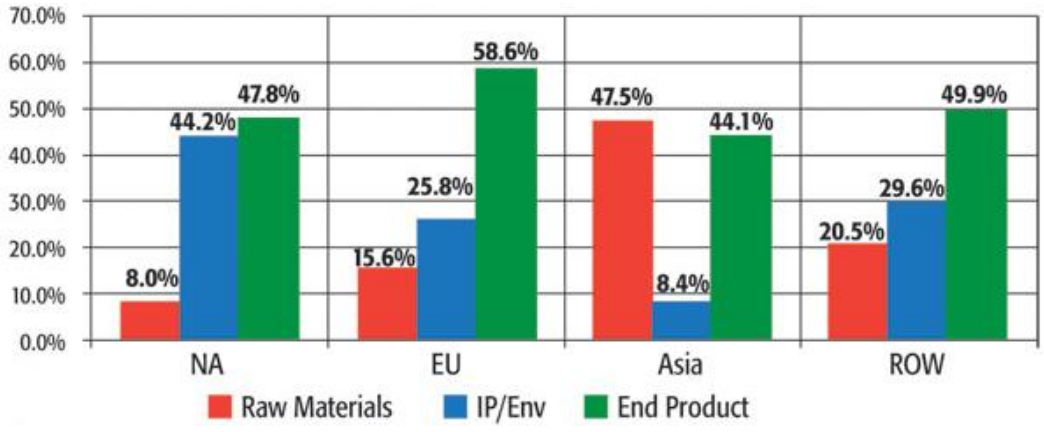

Figure 9. Collection of the pathogens sorted by production stage and by geographic area.

Food Fraud Prevention Market

The test for the detection of the amplification of target nucleic acid sequence is also an instrument to support the genetic traceability of the products. The same technology can be used to verify if the product is exactly what the producers claim; this is obviously necessary mainly for processed food, such as launch meat or filets, whose appearance doesn't allow to recognize the original product.
IIT solution is a valid option to fight Food Fraud. Food Safety Magazine (Trends and Solutions in Combating Global Food Fraud, March 2014) reports that according to the World Customs Organization, food fraud is costing $49 billion annually.
Food fraud is a concept which gathers different unlawful activities (Fig.10).

Figure 10. Substitution and dilution are very common form of food fraud.

The motivation behind food fraud is generally economical: the purpose is to increase the apparent value of the product or reduce the cost of its production. The substitution of ingredients is a common form of food fraud: for instance, spices and fish are substituted by less precious ingredients.
In 2012 EMA, the European Medicines Agency, has defined a list of problematic ingredients (Fig.11).

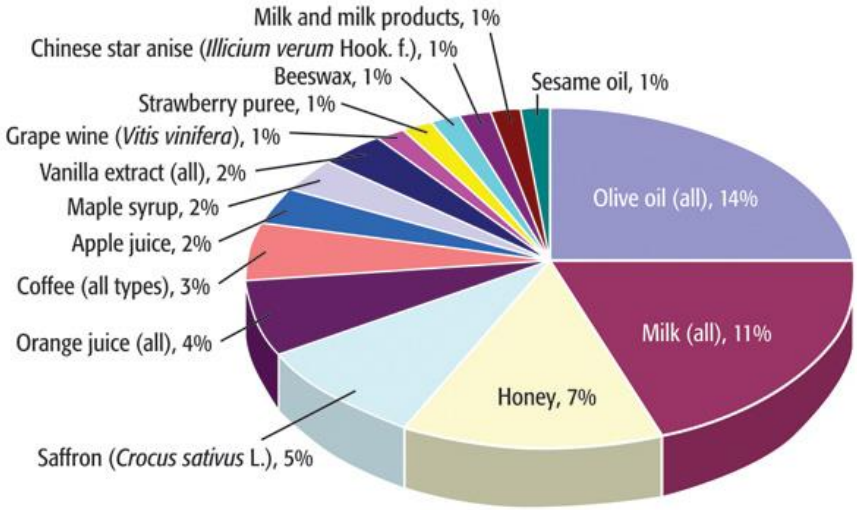

Figure 11. The 15 most problematic ingredients by EMA (European Medicines Agency, 2012) and their incidence (%) in overall fraudulent activities.

Commercial solutions for the prevention of food fraud are expensive and sometimes ineffective. As a consequence, the complete traceability of the food is a difficult goal to achieve through existing technologies. Under EU law, "traceability" means the ability to track any food, feed, food-producing animal or substance that will be used for consumption, through all stages of production, processing and distribution (Fig.12).

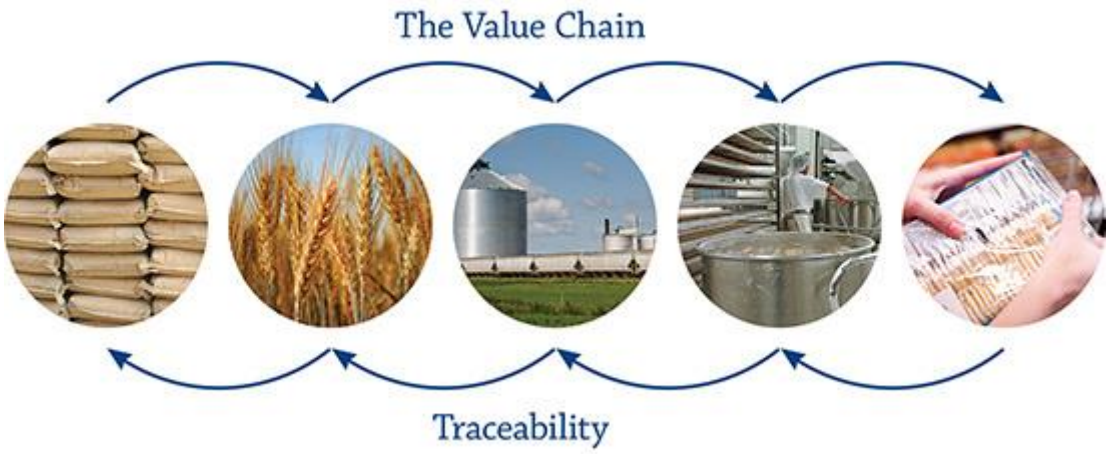

Figure 12. Traceability involves different players along the value chain, from producer to customer.

Technology provides every player with solutions to achieve a complete internal traceability, while the traceability beyond the boundaries of each company is still a challenge. Traditional technologies for this goal are RFI, GPS, infrared and similar; genetic traceability can offer a valid support and close the gaps.
According to the report by Markets & Markets "*Food Traceability Market by Technology (RFID, GPS, Barcode, Infrared, Biometric), End User (Manufacturer, Warehouse, Retailer, Government), Application (Fresh food Produce, Meat & Poultry, Seafood, Dairy, Beverage) & Region - Global Trend & Forecast to 2019*", the food traceability market is projected to grow at a CAGR of about 9% to reach $14 billion by 2019. In 2013, North America was the largest market for food traceability. Asia-Pacific is projected to be the fastest-growing market for food traceability during the review period. This is driven by the technological advancement and growing concern for food safety among consumers in developing countries such as India and China.

Molecular biology reagents market

According to the report by Markets & Markets "*Molecular Biology Enzymes and Kits & Reagents Market by Product (Kits & Reagents, Enzymes), Application (PCR, Sequencing, Cloning), End User (Academic & Research Institutes, Hospitals & Diagnostic Centers) - Trends & Global Forecasts to 2021*", the molecular biology enzymes and kits & reagents market is projected to reach USD 12.69 Billion by 2021 from USD 5.77 Billion in 2016, growing at a CAGR of 17.1% during the forecast period of 2016 to 2021. Growth in molecular biology enzymes and kits & reagents market can be attributed to the technological advancements in the life science industry, increased research activities in the pharmaceutical and biotechnology sector, rising incidences of infectious diseases and genetic disorders, and successful completion of human genome project. On the other hand, privacy issues related to genetic information and unfavorable reimbursement

scenario for genetic testing are expected to restraint the growth of the molecular biology reagents market during the forecast period.
This market is expected to grow equally in the three major areas: North America, Europe and Asia. (Fig.13)

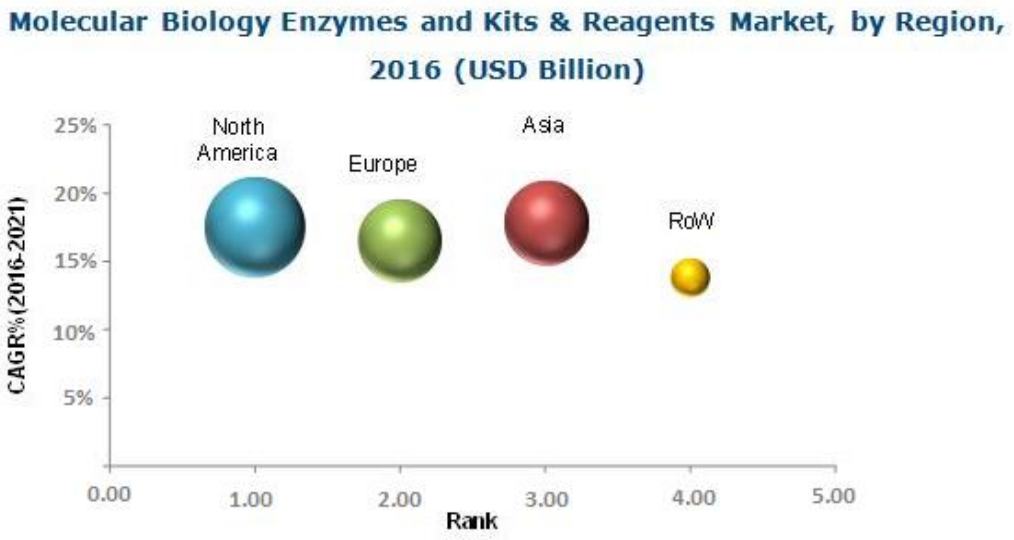

Figure 13. North America slightly leads the market. CAGR in the different areas are also comparable.

The main players of this market are the following ones:

- Manufacturing companies of molecular biology enzymes and kits & reagents
- Suppliers and distributors of molecular biology enzymes and kits & reagents
- Research institutes and academic centers
- Pharmaceutical and biopharmaceutical companies
- Biotechnology companies

COMPETITIVE SCENARIO

IIT solutions have several advantages over existing commercial technology, which have been partially described in the document. A brief analysis of the positioning of the two patented solution is reported below. Besides, a list of the companies which are active in the markets under analysis is available.

1) Detection of the amplification of a target nucleic acid sequence.

IIT colorimetric tests have at least the following advantages over competitive technologies: cost effectiveness, rapidity and no need for specific instrumentation. As a consequence, they are suitable for frequent and almost on-field test activities.
Moreover, these tests are superior than other colorimetric tests in scientific literature:

- The change of color is more evident
- The functionalized golden nanoparticles are not dependent on the target

Accordingly, these tests are also highly sensitive and universal, suitable for the detection of the amplification of any target.
Genetic food traceability works slightly differently, although the test is based on the same patent.
Standard technologies that allow genetic traceability of food are currently employed in traditional diagnostics, but requires expensive instrumentation or time consuming procedures, and thus are not routinely used for food analysis. Besides, their cost hampers their deployment to the large scale.
In the table below IIT solution is compared to other technologies:

	Applicable to degraded material	Low DNA requirement	Simple protocol	Mixture detection	Time efficient	No prior knowledge required	Reproducible between labs
Hybridization	✓			✓			
Species-specific primer	✓	✓	✓	✓	✓		✓
RFLP		✓	✓		✓	✓	✓
SSCP		✓			✓		
RAPD		✓	✓		✓		
Traditional sequencing	✓	✓	✓		✓	✓	✓
DNA barcoding	✓	✓	✓		✓	✓	✓
IIT solution	✓	✓	✓	✓	✓		✓

IIT solution has competitive advantages over the other technologies and, above all, is far less expensive;

2) Detection of the contamination with nucleases

The test kit for the detection with nucleases have the following advantages over competitive technologies:
- No fluorimeter or UV device is needed for a naked-eye detection
- It is suitable for colorful solutions (although the sensitivity is partially reduced)
- It detects both endonucleases and exonucleases

In the table below, IIT solution is compared to other commercial products already on the market.

	Instrument -free	Universal	Time saving	Simple procedure	Low cost	No nuclease in positive ctrl	No -20°C storage / dark handling	Sensitivity (LOD)
G Biosciences		Only RNAses			✓	✓	✓	1000pg
Jena Biosciences		✓	✓	✓	✓			4pg
MO BIO Laboratories		Only RNAses			✓	✓	✓	2500pg
New England Biolabs		Only RNAses			✓	✓		N/A
Thermo Fisher		✓	✓	✓	Only large formats			10pg
Indumy						✓	✓	4pg
Sigma Aldrich	✓			✓	✓	✓	✓	N/A
IIT Solution	✓	✓	✓	✓	✓	✓	✓	4 pg

In comparison with the commercial products, the test developed at IIT is highly competitive.

Leading Companies in Food Safety Market

The following list contains a sample of companies which are active in the Food market. Different players along the supply chain could be interested in IIT technology for testing the food safety. The list involves many Italian players.

Food manufacturers

- Amadori (Italy, http://www.amadori.it/)
- Barilla (Italy, http://www.barilla.it/)
- Conserve Italia (Italy, http://www.conserveitalia.it/index.php/it/)
- Danone (France, http://www.danone.com)
- Ferrero (Italy, https://www.ferrero.it/)
- Galbani (Italy, http://www.galbani.it/)
- General Mills (USA, www.generalmills.com/)
- Granarolo (Italy, http://granarolo.it/)
- Gruppo Cremonini (Italy, https://www.cremonini.com/)
- Kellogg Italia (Italy, http://www.kelloggs.it/it_IT/home.html)
- Mars Italia (Italy, http://www.mars.com/italy/it/)
- Mondelez International (USA, http://www.mondelezinternational.com/)
- Nestlè Italiana (Italy, http://www.nestle.it/)
- Parmalat (Italy, http://www.parmalat.it/)
- Pepsico (USA, http://www.pepsico.com/)
- Unilever Italia (Italy, https://www.unilever.it/)

Testing and certification companies

- 3M Italia (Italy, http://www.3mitalia.it/)

- AB Analitica (Italy, https://www.abanalitica.it/)
- Bioagricert (Italy, http://www.bioagricert.org/)
- Certified Laboratories (USA, http://certified-laboratories.com/)
- CSI (Italy, http://fpm.csi-spa.com/it/)
- EMSL Analytical (USA, http://foodtestinglab.com/)
- Intertek Italia (Italy, http://www.intertek.it/)
- LabAnalysis (Italy, http://www.labanalysis.it/)
- Mérieux NutriSciences Italia (Italy, http://www.merieuxnutrisciences.it/it/ita)

Packaging companies

- Praxair-Rivoira (Italy, http://www.rivoiragroup.it/it-it)

Italian Consortia and food and beverage associations

- Associazione Industriali delle Carni e dei Salumi (Italy, http://www.assica.it/)
- Associazione Italiana Consorzi Indicazioni Geografiche (Italy, http://www.aicig.it/)
- Associazione Nazionale Conservieri Ittici e delle tonnare (Italy, http://tonno360.it/)
- Consorzio del Prosciutto di Parma (Italy, http://www.prosciuttodiparma.com/)
- Consorzio per la Tutela del Formaggio Gorgonzola DOP (Italy, http://www.gorgonzola.com/)
- Consorzio Tutela Grana Padano (Italy, http://www.granapadano.it/)
- Federalimentare (Italy http://www.federalimentare.it/)
- Federdistribuzione (Italy, http://www.federdistribuzione.it/)
- Federvini (Italy, www.federvini.it)

Italian Mass retailers

- Auchan (Italy, http://www.auchan.it/)
- Bennet (Italy, http://www.bennet.com/)
- Conad (Italy, http://www.conad.it/)
- Coop Italia (Italy, http://www.e-coop.it/index.html)
- Esselunga (Italy, http://www.esselunga.it/cms/homepage.html)
- Sogegross (Italy, http://www.sogegross.it/)

Leading conmpanies in the market of molecular biology reagents

- Agilent Technologies (USA, http://www.agilent.com/home)
- Becton Dickinson Italia (Italy, http://www.bd.com/it/)
- F. Hoffmann-La Roche (Switzerland, http://www.roche.com/)
- Illumina (USA, http://www.illumina.com/)
- Jena Biosciences (Germany, https://www.jenabioscience.com/)
- Merck KGaA (Germany, http://www.merckgroup.com/en/index.html)

- New England Biolabs (USA, https://www.neb.com/)
- Prodotti Gianni (Italy, http://www.prodottigianni.it/)
- Promega Italia (Italy, https://ita.promega.com/)
- QIAGEN N.V. (Germany, https://www.qiagen.com/it/)
- Sigma Aldrich (USA, https://www.sigmaaldrich.com/)
- Takara Bio Inc. (Japan, http://www.takara-bio.com/)
- Thermo Fisher Scientific ((USA, http://www.thermofisher.com/it/en/home.html)

FOR FURTHER READING

- Paola Valentini, Pier Paolo Pompa
  "Gold nanoparticles for naked-eye DNA detection: smart designs for sensitive assays"
  RSC Adv., 2013,**3**, 19181-19190
  DOI: 10.1039/C3RA43729A

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

This report was composed by the Business and Financial Analysis Office – Technology Transfer IIT (technology.transfer@iit.it)