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# Nanotechnologies and Smart Systems for the Early Diagnostics

June 11 – 12, 2019  
CNR, Bologna (IT)

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## Version History

Version	Date	Contributor	Description
1.0.0	11/06/2019	Fabio Ugolini	Document created
1.1.0	9/07/2019	Fabio Ugolini	Document circulated
1.1.1	10/09/2019	Fabio Ugolini	Comments integrated – documents closed and circulated as “Nanotechnologies and Smart Systems for the Early Diagnostics – Proceedings”

## Introduction

The workshop “Nanotechnologies and Smart Systems for the Early Diagnostics” was organized in the framework of the H2020 MADIA (Grant Agreement N° 732678), to foster the dialogue between actors from academy, industry and civil society, on technological trends and needs in the field of early diagnosis

### MADIA in a nutshell

MADIA is developing a highly sensitive device for the early diagnosis of neurodegenerative disease, capable of recognizing targeted biomarkers existing at low concentration in treated cerebrospinal fluid (CSF) or blood samples. The device has been initially thought for the diagnosis of Alzheimer.

Four established biomarkers are currently used to predict Alzheimer:  $A\beta_{40}$ ,  $A\beta_{42}$ , *Total Tau (T-Tau)* and *Phosphorylated Tau (P-Tau)*. High level of *T-Tau* and *P-Tau*, in combination with low level of  $A\beta_{40}$  or low  $A\beta_{42}/A\beta_{40}$  ratio in CSF, is an indicator used for staging Alzheimer, including Mild Cognitive Impairment (MCI).

The device uses magnetic nanoparticles (MNPs) biofunctionalized with antibodies or aptamers, to conjugate the Alzheimer biomarkers in a biological sample. The device can concentrate the MNP-biomarker aggregates by 5-6 orders of magnitude. The concentrated sample is then directed through a microfluidic channel lined with magnetic sensors, which are in turn able to detect the aggregates and, thus, the Alzheimer biomarkers. Ideally, the device will increase the threshold sensitivity for the detection of biomarkers towards femtograms/ml, three orders of magnitude greater than the state of the art.

**Table 1.1:** Organizations involved in MADIA

Organisation	Acronym
Consiglio Nazionale delle Ricerche (coordinator)	CNR
Biodevice Systems SRO	BIOSYS
European Brain Research Institute	EBRI
I+ SRL	I+
Innova SRL	INNOVA
Scriba Nanotecnologie SRL	SCRIBA
Servizo Galego de Saude	SERGAS
Universidad de Santiago de Compostela	USC
Universitaet Bielefeld	UNIBI
University of Brighton	UoB

# Agenda

## June 11<sup>th</sup>

	Chairs: Dr. Fabio Ugolini, Dr. Giulia Foschi	
10:00 – 10:30	Registration	
10:30 – 11:00	<b>Welcome and Introduction</b>	<b>Dr. Valentin Alek Dediu</b> <i>MADIA coordinator</i>
11:00 – 11:45	<b>Tutorial lecture: “Parkinson’s Disease, Alzheimer disease and other less common neurodegenerative diseases”</b>	<b>Prof. Giovanni Fabbrini</b> <i>Chair: Dr. Mara d’Onofrio</i>
11:45 – 12:30	<b>Tutorial lecture – “Nanotechnology, plasmonics and microfluidics: challenging applications in clinical diagnosis”</b>	<b>Prof. Giuseppe Spoto</b> <i>Chair: Prof. Matteo Santin</i>
12:30 – 14:00	Lunch break	
14:00 – 14:30	<b>Virtual Supermarket, a smart diagnostic procedure</b>	<b>Prof. Magda Tsolaki</b>
14:30 – 15:00	<b>Alzheimer’s A<math>\beta</math> Oligomers: new insights into nanobody-based detection and targeting</b>	<b>Dr. Giovanni Meli</b>
15:30 – 16:00	<b>Lab-on-chip platforms for chemical and biological analysis</b>	<b>Prof. João Pedro Conde</b>
16:00 – 16:30	<b>Wearable diagnostic devices: the new frontier for medical care</b>	<b>Dr. Sabrina Conoci</b>
16:00 – 16:30	Coffee Break	
16:30 – 18:00	<p><b>Panel: “Nanotechnology for Innovative Diagnostics: possible strategies for EU research efforts”</b></p> <p>Topics:</p> <ol style="list-style-type: none"> <li>1) Early diagnostics – medical/patient needs, societal needs</li> <li>2) Nanotechnologies for early diagnostics</li> <li>3) Ultrasensitive vs fast &amp; simple – laboratory vs wearable</li> <li>4) Networking and funding strategies: H2020, Horizon Europe, other schemes</li> </ol>	<p>Moderator: <b>Dr. Aleardo Furlani</b></p> <p>Panelists:  <b>Prof. Giovanni Fabbrini</b>  <b>Prof. João Pedro Conde</b>  <b>Dr. Sabrina Conoci</b>  <b>Dr. Valentin Alek Dediu</b>  <b>Dr. Federica Lodato</b>  <b>Dr. Silvia Pascale</b>  <b>Prof. Magda Tsolaki</b>  <b>Prof. Antonio Ambrosi</b>  <b>Dr. Andreas Lymberis</b></p>

## June 12th

Chairs: Dr. Fabio Ugolini, Dr. Giulia Foschi		
9:30 – 10:00	<b>Wearable organic biosensor for real-time monitoring of biomarkers</b>	<b>Prof. Beatrice Fraboni</b>
10:00 – 10:30	<b>Chemiluminescence-based biosensors for diagnostic applications in space missions</b>	<b>Prof. Mara Mirasoli</b>
10:30 – 11:00	Coffee break	
11:00 – 11:30	<b>CMOS-based nanoelectrode array sensors</b>	<b>Dr. Luca Selmi</b>
11:30 – 12:00	<b>30 years of miltenyi biotec: a brief history of MACS technology, from cell separation to cell analysis, imaging and therapy</b>	<b>Dr. Jonathan Fauerbach</b>
12:00 – 12:30	<b>From design to marketing of an IVD - How to adapt your company to the new European Regulation</b>	<b>Dr. Luca Bracchi</b>
12:30 – 12:40	<b>Closing remarks</b>	<b>Dr. Fabio Ugolini</b>

## Speakers and Panelists

	Andreas Lymberis <a href="#">European Commission</a>	Andreas Lymberis is a physicist, post-graduated with a Ph.D. in biomedical engineering and sciences (1990, Paris, France). He worked for more than 20 years as a researcher/engineer and R&D manager in biomedical technology and health telematics. He is the Head of Sector "Wearables & Bioelectronics" at the European Commission since 2016
	Antonio Ambrosi <a href="#">University of Foggia</a>	Antonio Ambrosi is a resident surgeon and professor at the University of Foggia
	Beatrice Fraboni <a href="#">University of Bologna</a>	Beatrice Fraboni is a Professor of Physics. In 2000 she joined the Faculty of Physics at the University of Bologna where. Her research activity focuses on the analysis and characterization of the electrical transport properties of organic and inorganic semiconducting materials and of advanced (bio)electronic devices.
	Federica Lodato <a href="#">Italian Red Cross</a>	Federica Lodato is a Regional Secretary of the Italian Red Cross
	Giovanni Fabbrini <a href="#">Sapienza University</a>	Giovanni Fabbrini is a Professor in Neurology and Psychiatry, and manager and responsible of the rare disease center "Distonia e altri disturbi del movimento dell'adulto" at the Hospital Umberto I in Rome.

	<p>Giovanni Meli  <a href="#">EBRI – European Brain Research Institute</a></p>	<p>Giovanni Meli is an expert researcher in neuroscience, neurodegeneration and Alzheimer’s disease. He is group Leader at the European Brain Research Institute since 2012. Giovanni and his group are carrying out an Alzheimer’s Association research grant on <math>\beta</math>-Amyloid peptide oligomer targeting. In addition to that he collaborates to many national and international research projects, among which the Human Brain Project.</p>
	<p>Giuseppe Spoto  <a href="#">University of Catania</a></p>	<p>Giuseppe Spoto is professor of analytical chemistry. He has been coordinating the EU project <a href="#">ULTRAPLACAD</a> on early diagnosis of cancer</p>
	<p>João Pedro Conde  <a href="#">University of Lisbon</a>  <a href="#">INESC MN</a></p>	<p>João Pedro Conde is president of the Department of Bioengineering, and professor at the University of Lisbon. He is co-responsible for the Thin Film MEMS and BioMEMS research group and a director of INESC Microsystems and Nanotechnologies.</p>
	<p>Jonathan Fauerbach  <a href="#">Milteny Biotech</a></p>	<p>Jonathan Fauerbach is group leader in the Chemistry department at Miltenyi Biotec. His group is focused on the research on magnetic and fluorescent nanomaterials, as well as conjugation strategies to biomolecules, and their applications on cell analysis, imaging and cell separation.</p>
	<p>Luca Bracchi  <a href="#">Thema Srl</a></p>	<p>Luca Bracchi works since 2010 on development and commercialization of biomedical devices. Since 2017 he is Product Manager QA\RA (Quality Assurance \ Regulatory Affairs) at Thema-Med and helps companies to navigate the regulatory maze connected to the commercialization of medical devices.</p>
	<p>Luca Selmi  <a href="#">University of Modena and Reggio Emilia</a></p>	<p>Luca Selmi is professor of electronics at the University of Modena and Reggio Emilia. He was coordinator in several international research projects of the European Union and of the Italian Ministry for University Education and Research. He started and/or supervised research contracts with a Semiconductor companies worldwide, including Philips, Infineon, STM, NXP</p>
	<p>Magda Tsolaki  <a href="#">Aristotle University of Thessaloniki</a></p>	<p>Magda Tsolaki is professor of neurology and head of the neurology department at the Aristotle University of Thessaloniki. She the founder and chair of the Greek Alzheimer Association and the Greek Federation of Alzheimer’s Disease (AD) in 2007, and the director two Public Dementia Units for outpatients.</p>
	<p>Mara Mirasoli  <a href="#">University of Bologna</a></p>	<p>Mara Mirasoli is professor in analytical chemistry at the University of Bologna. She is the vice-director of the Chemistry Department and she is associated to the centres for industrial research on “Renewable sources, environment, sea, and energy”, and on “Aeronautics, space, and mobility” of the University of Bologna</p>
	<p>Sabrina Conoci  <a href="#">ST Microelectronics</a></p>	<p>Dr. Sabrina Conoci covered several R&amp;D positions in the field of nano-molecular devices, biosensors and biotechnologies. She is currently R&amp;D Manager of the Advanced Sensor Technologies team at ST Microelectronics</p>

	<p>Silvia Pascale  <a href="#">Sorin Group Italia (LivaNova)</a></p>	<p>Silvia Pascale is a senior manager at Sorin Group Italia. There she has been involved in the management of more than 40 national and international research projects related to the cardiovascular system and biomaterials</p>
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## Chairs

	<p>Aleardo Furlani  <a href="#">INNOVA Srl</a></p>	<p>Aleardo Furlani is founder and CEO of INNOVA Srl, a startup incubator and innovation service provider. Since 1996 he works on international capacity building initiatives on topics such as internationalization, technology transfer, marketing and innovation processes</p>
	<p>Fabio Ugolini  <a href="#">INNOVA Srl</a></p>	<p>Fabio Ugolini is a technology transfer officer and project manager at INNOVA Srl where he contributes to develop the financing, communication, dissemination and commercialization strategies of several international research projects</p>
	<p>Giulia Foschi  <a href="#">Scriba Nanotecnologie</a></p>	<p>Giulia Foschi is a senior researcher at Scriba Nanotecnologie. She focuses on nano- and micro-fabrication processes, fabrication of microfluidic devices, electrochemistry, unconventional lithography, fabrication of biomolecules and functional materials, functionalization of surfaces and nanoparticles, self-assembly monolayer and drug delivery</p>
	<p>Mara d'Onofrio  <a href="#">EBRI – European Brain Research Institute</a></p>	<p>Mara d'Onofrio is the head of the genomic facility at the European Brain Research Institute, and a researcher at the Institute of Translational Pharmacology. Her major expertise is molecular and systems neurobiology and neurodegeneration, particularly regarding the roles of Nerve Growth Factor (NGF) and neurotrophins in the Central Nervous System,</p>
	<p>Matteo Santin  <a href="#">University of Brighton</a></p>	<p>Matteo Santin is professor of tissue regeneration and leads both BrightSTAR and the Brighton Centre for Regenerative Medicine. He is president of the European Society for Biomaterials and has 25 years of experience in the field of biomaterials and tissue engineering.</p>
	<p>Valentin Alek Dediu  <a href="#">University of Bologna</a></p>	<p>Alek Dediu leads the research group Magnetic Nanostructures for Spintronics and Nanomedicine at CNR-ISMN-Bologna. He is currently the coordinator of the MADIA project, and has been coordinating three other international projects: OFSPIN, HINTS, and MAGISTER.</p>

# Attendance

Organization	Type	Country
Aristotle University of Tessaloniki	ACA	GR
Biodevice Systems SRO	IND	CZ
Consiglio Nazionale delle Ricerche	ACA	IT
European Brain Research Institute	ACA	IT
European Commission	CIV	BE
I+ SRL	IND	IT
INESC MN	IND	PT
Innova SRL	IND	IT
Italian Red Cross	CIV	IT
Militeny Biotech	IND	DE
Scriba Nanotecnologie SRL	IND	IT
Servizo Galego de Saude	CIV	ES
Sorin Group Italia	IND	IT
ST Microelectronics	IND	CH
Thema Srl	IND	IT
Universidad de Santiago de Compostela	ACA	ES
Universitaet Bielefeld	ACA	DE
University "Sapienza"	ACA	IT
University of Bologna	ACA	IT
University of Brighton	ACA	UK
University of Catania	ACA	IT
University of Foggia	ACA	IT
University of Lisbon	ACA	PT
University of Modena / Reggio Emilia	ACA	IT

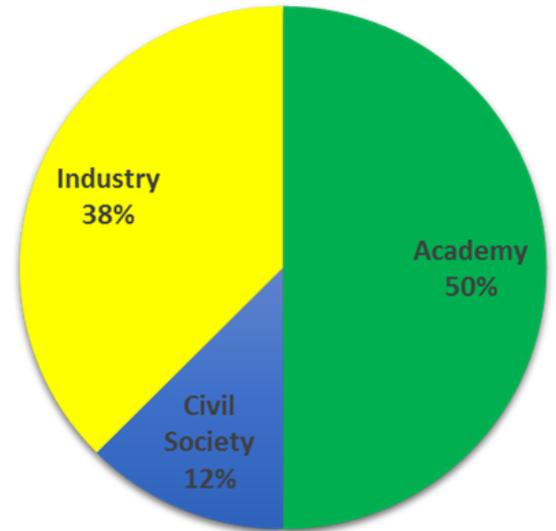


Figure 1: attendance at the workshop by type of organization and country of origin. **ACA** = Academia; **IND** = Industry; **CIV** = Civil Society

## Highlights

<b>Parkinson's Disease, Alzheimer disease and other less common neurodegenerative diseases</b>	Prof. Giovanni Fabbrini	
An account of the challenges in diagnosing of neurodegenerative diseases. Those classify in diseases with motor disfunctions ( <i>e.g.</i> Parkinson's disease), cognitive disfunctions ( <i>e.g.</i> Alzheimer's disease), and motocognitive disfunctions ( <i>e.g.</i> Lewy body dementia). A classification exists also on by main protein abnormality ( <i>e.g.</i> $\alpha$ -synuclein, $\beta$ -amyloid, Tau protein). Due to the complexity of the diagnosis of these disease at the early stage, better knowledge and use of biomarker indicators might facilitate and complement traditional neuropsychological testing.		
<b>Nanotechnology, plasmonics and microfluidics: challenging applications in clinical diagnosis</b>	Prof. Giuseppe Spoto	
Early diagnostics might find its holy grail in liquid biopsies in plasma. Combinations of discoveries in surface plasmon resonance imaging, nanotechnology and droplet microfluidic might make it possible to diagnose complex disease with a blood test. The H2020 project ULTRAPACAD showed potential for the diagnosis of cancer using DNA markers in blood. One of the current challenges is being able to capture the relatively rare biomarkers in the early stage of the disease		
<b>Virtual Supermarket, a smart diagnostic procedure</b>	Prof. Magda Tsolaki	
Self-diagnosis of neurodegenerative disease is becoming a reality through "Serious Games", which are videogames especially designed to quantify behaviors which might be revealing the onset of a disease. Further development goes towards designing software and tools which are both elderly-friendly and predictive enough to be complementary to traditional neuropsychological testing		
<b>Alzheimer's A<math>\beta</math> Oligomers: new insights into nanobody-based detection and targeting</b>	Dr. Giovanni Meli	
Nanobodies, which are antibodies capable to penetrate inside human cells, have high potential as imaging tools for the detection of biomarker indicators of neurodegenerative diseases		
<b>Lab-on-chip platforms for chemical and biological analysis</b>	Prof. João Pedro Conde	
Advanced lab-on-a-chip platforms based on a simplified microfluidic architecture allow for portable and highly-sensitive detection of biomarkers which would normally require bulkier assays and equipment. INESC-MN is working on a simple device for detecting gamma-interferon in blood for antibody and therapy monitoring.		
<b>Wearable diagnostic devices: the new frontier for medical care</b>	Dr. Sabrina Conoci	
From the industrial standpoint, there is high interest in wearable diagnostic devices exchanging real-time information through the Internet of Things. The closed loop glucose monitoring systems are currently one of the most important the market driver in this field . Silicon and derivatives are very attractive materials for wearable applications, since they offer integrated technologies and smart sensor devices such as silicon photo multipliers. The challenges in the field are clinical validation and regulatory approval (currently there a very few products that are authorize for the market), selection of biomarkers, improvement of accuracy,		

<p>system integration and data security. Estimated market opportunity is 150 million in 2016, 2.86 billion in 2025.</p>		
<p><b>Panel: Nanotechnology for Innovative Diagnostics: possible strategies for EU research efforts</b></p>	<p>Various</p>	
<p>Good surrogate markers (<i>i.e.</i> biomarkers) are needed, in addition to early diagnosis, also to demonstrate that therapies are working. Multiple Sclerosis therapy, for example, can rely on powerful surrogate markers. The regulatory burden is however a challenge for all the new technologies. Academia in research projects must engage early both the manufacturer and the regulatory agency, in order to clarify the requirements to enter clinical trials and, consequently, the market.</p> <p>Ultrasensitive approaches and Fast &amp; Simple approaches are not mutually exclusive. However, solutions must be tailored towards the intended end users: emergency responders would favour Fast &amp; Simple approaches that gives a “yes or no” measurement, and wearable devices that produce a lot of data continuously might not require the same level of sensitiveness of an <i>in-vitro</i> one-time measurement.</p> <p>Cooperation between academia, industry, civil society, policy maker and end users is going to be increasingly a requirement in European research projects. Consortia should include actors from all these groups. Neurodegenerative disease and early diagnosis are going to be topical in Horizon Europe, which is going to have a budget of 7.5 billion € for projects on health and wellbeing</p>		
<p><b>Wearable organic biosensor for real-time monitoring of biomarkers</b></p>	<p>Prof. Beatrice Fraboni</p>	
<p>The next generation of wearables will include textile electronic sensors, such as chemical biosensors, which can be directly fabricated onto fabrics, in apparel and clothing accessories. These wearables operate as real-time electronic devices, rely on a very low amount of test liquid (<i>e.g.</i> sweat) and require a very low power supply.</p>		
<p><b>Chemiluminescence-based biosensors for diagnostic applications in space missions</b></p>	<p>Prof. Mara Mirasoli</p>	
<p>End-users of diagnostic devices may include categories with very special needs, such as astronauts operating in zero-G. Diagnosis requiring fluid specimens is particularly challenging, and non-invasive sampling is a requirement. Oral fluid sampling, lateral flow immunoassays and chemiluminescence detection were exploited to develop a point-of-need biosensor used onboard the ISS for the measurement of salivary cortisol, which is a biomarker of chronic stress during long space missions</p>		
<p><b>From design to marketing of an IVD - How to adapt your company to the new European Regulation</b></p>	<p>Dr. Luca Bracchi</p>	
<p>The new European <i>in-vitro</i> Diagnostic Regulation will require the manufacturer of diagnostic devices to adapt. The transition period lasts from 2017 to 2022. The European Commission is implementing the European databank on Medical Device (EUDAMED) to guide the regulatory process. The new regulation expands the list of the IVDs covered to include high-risk devices, near patient / point-of-care devices, and genetic tests. It introduces the figure of “sponsor” for clinical investigations, and new requirements for labelling, post-marketing surveillance and vigilance</p>		



Figure 2: Alek Dediu and Aleardo Furlani discussing the panel



Figure 3: the panelists



**Figure 4:** Dr. Sabrina Conoci gives the industrial perspective on early diagnostics devices



**Figure 5:** Prof. João Pedro Conde and Prof. Giovanni Fabbrini discuss the importance of surrogate biomarkers