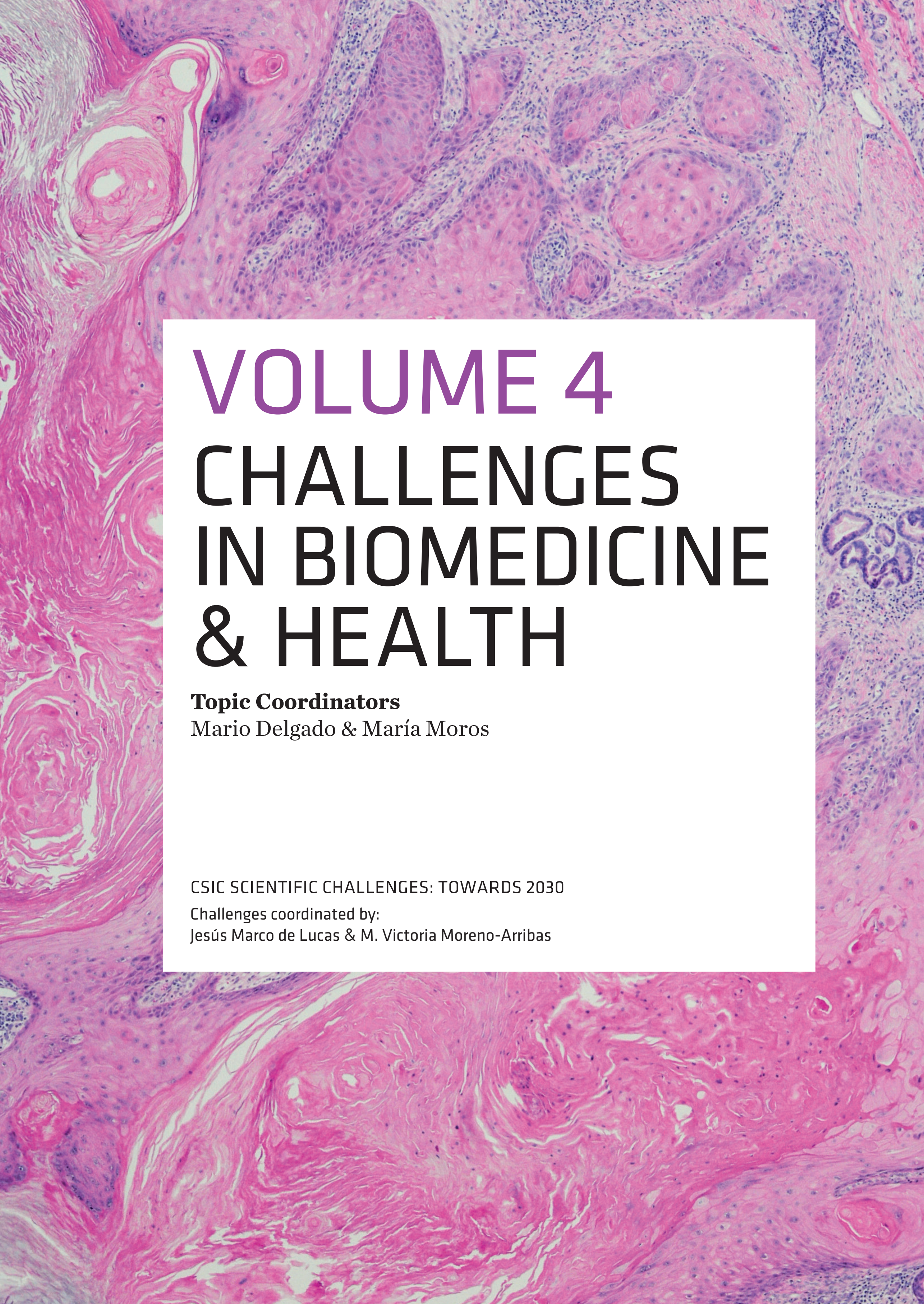

VOLUME 4
CHALLENGES IN BIOMEDICINE & HEALTH

Topic Coordinators
Mario Delgado & María Moros

CSIC SCIENTIFIC CHALLENGES: TOWARDS 2030
Challenges coordinated by:
Jesús Marco de Lucas & M. Victoria Moreno-Arribas

VOLUME 4

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CSIC SCIENTIFIC CHALLENGES: TOWARDS 2030

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CSIC SCIENTIFIC CHALLENGES: TOWARDS 2030

What are the major scientific challenges of the first half of the 21st century? Can we establish the priorities for the future? How should the scientific community tackle them?

This book presents the reflections of the Spanish National Research Council (CSIC) on 14 strategic themes established on the basis of their scientific impact and social importance.

Fundamental questions are addressed, including the origin of life, the exploration of the universe, artificial intelligence, the development of clean, safe and efficient energy or the understanding of brain function. The document identifies complex challenges in areas such as health and social sciences and the selected strategic themes cover both basic issues and potential applications of knowledge. Nearly 1,100 researchers from more than 100 CSIC centres and other institutions (public research organisations, universities, etc.) have participated in this analysis. All agree on the need for a multidisciplinary approach and the promotion of collaborative research to enable the implementation of ambitious projects focused on specific topics.

These 14 "White Papers", designed to serve as a frame of reference for the development of the institution's scientific strategy, will provide an insight into the research currently being accomplished at the CSIC, and at the same time, build a global vision of what will be the key scientific challenges over the next decade.

VOLUMES THAT MAKE UP THE WORK

1. *New Foundations for a Sustainable Global Society*
2. *Origins, (Co)Evolution, Diversity and Synthesis of Life*
3. *Genome & Epigenetics*
4. *Challenges in Biomedicine and Health*
5. *Brain, Mind & Behaviour*
6. *Sustainable Primary Production*
7. *Global Change Impacts*
8. *Clean, Safe and Efficient Energy*
9. *Understanding the Basic Components of the Universe, its Structure and Evolution*
10. *Digital and Complex Information*
11. *Artificial Intelligence, Robotics and Data Science*
12. *Our Future? Space, Colonization and Exploration*
13. *Ocean Science Challenges for 2030*
14. *Dynamic Earth: Probing the Past, Preparing for the Future*

CSIC scientific challenges: towards 2030
Challenges coordinated by:
Jesus Marco de Lucas & M. Victoria Moreno-Arribas

Volume 4
Challenges in Biomedicine & Health

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CONTENIDO

ABSTRACT

A lesson that we have learned from the pandemia caused by coronavirus is that solutions in health require coordinated actions. Beside this and other (re)emerging infectious diseases, Spain and Europe are suffering a plethora of disorders that are currently acquiring epidemic dimensions, including cancer, rare diseases, pain and food allergies, among others. New tools for prevention, diagnosis and treatment need to be urgently designed and implemented using new holistic and multidisciplinary approaches involving researchers, clinicians, industry and all stakeholders in the health system. The CSIC is excellently positioned to lead and coordinate these challenges in Biomedicine and Health.

KEYWORDS

biomedicine | therapies | diagnostic tools | cancer | chronic diseases

CHALLENGE 8

ABSTRACT

New Methods for diagnostic tools and prevention is a wide and active area comprising groups across physics, chemistry, engineering and biomedicine. The area encompasses novel imaging techniques (optical, ultrasound, atomic force microscopy-based, and molecular imaging) and biosensing (chemical, biological, including microfluidic-based devices and biocompatible, biodegradable sensors). Biomarkers and physical and functional properties (at the cell, tissue and organ level) are used to guide personalized treatment and formulate preventive health measures. The groups of CSIC have contributed to results ranging from basic science to clinical translation and industry transfer.

KEYWORDS

diagnosis | prevention | biosensors

bioimaging | biomarkers

artificial inteligence | personalized medicine

CHALLENGE 8

NEW METHODS FOR DIAGNOSTIC TOOLS AND PREVENTION

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1. INTRODUCTION AND GENERAL DESCRIPTION

The area is highly interdisciplinary, with a wide range in areas of research, methodologies and applications. We have widely classified the contributions according to imaging modality for diagnostics, detection/screening methods, and prevention and personalized treatments.

1.1. Medical Imaging Techniques for diagnostics

Optical and Ultrasound Imaging

There is a need for non-invasive imaging instrumentation in the clinical environment that allows in vivo geometrical and functional imaging of organs and tissue at high resolution.

Optical technologies include Optical Coherence Tomography, Wavefront sensing, Adaptive Optics or Ocular Section Microscopy. Given the transparent nature in the eye, with relatively low scattering, these quantitative 3-D imaging techniques are highly suitable for fully non-invasive applications in ophthalmology. The Visual Optics and Biophotonics Lab (VIOBIO-LAB, IO-CSIC) is a worldwide leader in the area, supported by ERC Advanced Grants (PRESBYOPIA, SILK EYE); Coordinated H2020 Innovation Action IMCUSTOMEYE and Marie Curie ITNs, among others. Diagnostic tools in the eye have made the way to the clinic in the form of a wavefront-sensor autorefractor (Quicksee) and a Vision Simulator of presbyopic correction (SimVis), among others (Durr et al., 2014; Dorronsoro et al. 2016). Besides, the combination of imaging technologies with optical modeling and Finite Element Modelling, and Psychophysical/Perceptual quality metrics, allow new functional tests beyond those purely optical (for example corneal biomechanics), customized optical modeling to guide surgery, and the visual effects of optical manipulations (Marcos et al. 2017).

Ultrasound Imaging technologies outperform standard diagnostic technologies such as X-ray, as they do not use ionizing radiation, and can be more specific to diagnose certain pathologies with high incidence (such as breast cancer, particularly in radiologically dense breasts - 4 out of 10 women). In addition, ultrasound imagng techniques can be performed in the patient bed, resulting in a more comfortable and cost-effective exploration than magnetic resonance, computerized tomography, PET, etc. Three different groups at ITEFI-CSIC collaborate in the development of ultrasound imaging medical applications: the Group of Ultrasonic System and Technologies (ITEFI-CSIC), the Group of Ultrasound for the analysis of liquids and Bioengineering and the Group of signal processing in multichannel ultrasound systems. Their advances include automated acquisition and multimodal image (including doppler and elastography) to provide complementary information on the tissue (morphology, density, stiffness, etc), for applications in breast cancer (González-Salido et al., 2016); high resolution image acquisition at high frequency (Camacho, 2009) to study serous tissues and liquids in the body (for example to monitor meningitis in newborns (Jimenez et al. 2016; Elvira, 2019)); and the development of electronic systems for brain image in animal models.

Atomic Force Microscopy for Mechanobiology

The forces of mechanical origin at the cellular level are involved in growth regulation, cellular differentiation and tumor progression, therefore showing an important diagnostic potential. Mechanobiology addresses two main objectives: on one hand understanding the mechanism associated to the detection and response to mechanical forces by proteins, cells and tissues, and on the other hand solving the relationship between the mechanical state of a cell and its physiological state (Dufrêne et al., 2017; Guerrero et al., 2019). The Force-Tool Group at IMM-CSIC develops new methods based on Atomic Force Microscopy to dilucidate basic relations between the mechanical properties of cells and tissues and disease (particularly cardiovascular disease) and to develop early diagnostic tools for the clinic.

The Laboratory of Protein Nanomechanics at ICN-CSIC, also uses Single-Molecule Force Spectroscopy based on Atomic Force Microscopy for early diagnosis of amyloidogenic diseases, with the aim of identifying specific conformers that trigger the amyloid cascade (Hervas et al., 2012; Oroz et al., 2012 ; Weaber, 2012) and/or quantifying the conformational polymorphism observed in the amyloidogenic proteins (Fernández-Ramírez et al., 2018) and use either (or both of them) as molecular reporters for the propensity of forming pathological amyloid in samples of blood or cerebrospinal fluid from human probands.

Molecular imaging

Several groups at CSIC address improvements in Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) from different perspectives: improvements of clinical sensitivity, modeling of positron-tissue interaction, new detectors, and new nanoparticles for MRI and PET.

In particular: I3M-CSIC investigates the increase of image quality and clinical sensitivity in PET through both photo-electric and Compton effects, and develops new detectors for molecular Imaging and new high resolution PET for cardiovascular imaging with high temporal resolutions. The group has been successful in EU project turnovers (FP6, FP7 and ERC Advanced Grants) and technology transfer (spin-out Oncovision having deployed 30 clinical PET units, and Bruker BioSpin which commercializes pre-clinical PET units); The Radiation-Mater Interaction (RMI) Research Group at IFF-CSIC that studies positron-tissue interactions in scattered media (Stevens et al., 2018; Robson et al., 2015). The Image Reconstruction, Instrumentation and Simulations in Medical applications Group (IRIS) at IFIC-CSIC, which leads the development of Compton cameras for hadron therapy treatment monitoring in Europe, having developed a prototype to operate in a clinical environment and demonstrated the possibility of imaging the distribution of photons emitted by an irradiated material similar to human tissue (Solevi et al. 2016). The experimental nuclear physics groups at IEM-CSIC and IFIC-CSIC, which jointly develop a 3D proton- CT scanner with proton-range verification capabilities for real-time therapy monitoring, by minimizing image blurring due to multiple scattering (MSC) (Albiol et al., 2019; Ytre-Hauge et al., 2019). The Namomedmol Group (IQM-CSIC) develops nanoparticules for use in molecular imaging, in particular first combination of 68Ga and iron oxide nanoparticles for the combined use of T1-MRI and PET (used for the early in vivo detection of angiogenesis, microcalcifications, neutrophils and oxidised phospholipids) and iron oxide nanoparticles with enhanced properties as T1 (positive contrast) probes for magnetic resonance imaging in preclinical applications.

1.2. Biomarkers and Biosensors

Primary goals of the imaging techniques described above are the deployment of biomarkers for early disease diagnostics. For example, from Air Puff/Acoustic Stimulated Corneal Deformation Imaging the VioBio-Lab at IO-CISC obtains biomechanical biomarkers of corneal disease, or from Adaptive Optics/SimVis Simulation, perceptual quality markers of multifocal corrections of presbyopia, among others (Curatolo et al., 2020); from AFM, the ForceTool Group at ICMM-CSIC obtains nanomechnical biomarkers (elastic modulus or disipation coefficients) to track disease; or from Ultrasound Imaging, the Ultrasounds Groups at ITEFI obtain tissue stiffness from full angle elasticity as an indicator of tumor malignancy, or obtain a marker of the concentration of leukocytes in the cerebrospinal liquid as an indicator for meningitis.

Besides, other groups focus on the development of disease biomarkers to be applied in biosensor approaches. The ultimate goal is point-of-care applications and wearable devices to monitor health and disease. The Advanced Sensor Technology Group at ITEFI-CSIC develops chemical and biological sensors (resistive, surface acoustic waves, and magnetic) to detect markers (gaseous compounds) in the breath for early diagnosis of disease (Le Maout et al., 2018) (for example diabetes, kidney, liver or respiratory diseases), such as carbon monoxide (inflammation of the lung), dimethyl sulfide (liver disease), and nitric oxide (asthma), as well as surface acoustic wave sensors in combination with microfluidics to detect biological targets (Matatagui et al., 2014) (antibiotics, growth factors, etc.). The Biomedical Applications Group at IMB-CMM-CSIC develops biocompatible and biodegradable implants for neurological applications, and wearable devices (implants and external) for the real time and continuous monitoring, and early diagnosis for in vivo applications. Additionally, this group and the Chemical Transducers Group at IMB-CNM-CSIC develop chemical sensors integrated into microfluidic systems for applications of cellular studies, including single cell analysis and tissues, and for producing multiplexed analytical tools for simultaneous detection of biomarkers at the point-of-care. The HPLC-CE Lab of the Instrumental Analysis in Environment, Food and Health Group at IQOG-CSIC develops high resolution separation methods that reveal alterations in glycoproteins due to changes in their glycosylation or other post-translational modifications (PTMs) which are related to certain diseases and therefore can be used as a disease biomarker (other applications include measurement of the alteration of immunoglobulins in breast milk) (Farina-Gomez et al., 2017; Puerta et al., 2011). The Nucleic Acids Chemistry Group at IQAC-CSIC develops oligonucleotides for the functionalization of biosensors, including DNA capture probes based on DNA-clamps for triplex formation, DNA-directed inmbobilization probes, and derivatives for detection of thrombin (Aviñó et al., 2016; Oroval et al., 2013). In turn, the Structure of Nanometric Systems Group (ESISNA) at ICMM-CSIC produce chemically functionalized graphene with nucleic acid aptamers. These molecules (RNA or single-stranded DNA) can bind with high affinity and specificity to a given target molecule, for example to recognize a a viral protein or tumor markers (Bueno et al., 2019).

1.3. Machine Learning and Artificial Intelligence in medical diagnostics imaging and biomarkers

Imaging and selection of biomarkers benefit from machine learning and artificial intelligence. Several groups working on different imaging modalities count on resources in their teams for automated image processing. However, with the potentially large spatially and temporal datasets, potential integration of multimodal information, and potential for automated prognosis and diagnostics, machine learning and artificial intelligence hold promise to become critical across the field. The VioBio Lab Group uses automatic image processing for segmentation of ocular structures, image distortion correction and quantification in Optical Coherence Tomography and Ocular Section Microscopy. The ForceTool Group is already implementing big data and machine learning algorithms for rapid diagnostics, and the Ultrasonic System and Technologies Group has also identified deep learning algorithms as promising line for further exploiting the outcomes of the ultrasound-based imaging technique and is also working on artificial intelligence tools to aid in the diagnosis of COVID-19 disease using lung ultrasound images.

There are two groups which focus primarily on the development of machine learning and AI for medical imaging application. While the main application for these groups is MRI, all mentioned imaging modalities can benefit from these developments (conveniently adapted), to help radiologists and specialists in the quantification and detection of anomalies in the medical images. The Plasticity of Brain Networks at INA-CSIC combines multiple imaging modalities and texture analysis in machine learning platforms to define "disease signatures" in brain imaging, the generation of "functionalized biomarkers", and the use advanced imaging protocols and sophisticated mathematical models in diffusion imaging. The Medical Physics Group at IFIC-CSIC develops new AI algorithms for medical imaging, including the use of Annotated data, combination information from different medical devices, retrospective and device biased learning and continuous learning (De Santis et al., 2019a; De Santis et al., 2019b; De Santis et al., 2019c; Toschi et al., 2020).

1.4. Prevention and Treatment customization

The imaging and biomarker tools described above have an early diagnostic purpose but also the personalization of treatment and care. In many regards, the information gathered from those tools must serve to inspire treatments, guide surgery at the individual level, and in general, offer therapeutic solutions based on sound understanding of mechanisms underlying disease. We have grouped very diverse therapeutic solutions to a large range of medical conditions under this general section of prevention and treatment customization.

Custom implants

The technologies developed by VioBio Lab of the IO-CSIC for 3-D Quantification of ocular geometrical and biomechanical properties of a patient's eye lead to the generation of opto-mechanical customized model eyes that serve as platforms for virtual (cataract and corneal) surgery. Quantification of the cornea and crystalline lens has also stimulated bio-inspired implants for the correction of cataract and presbyopia (including the extended-depth-of-focus Isofocal IOL, licensed to/commercialized by PhysIOL, Inc and already implanted in patients) or the Accommodating IOL LightLensTM engaged by photobonding, among others (outputs of the ERC Advanced Grant Presbyopia and ERC Proof-of-Concept Grants OCT4IOL, SimVisSim and LightIOL). Also, new materials (more biocompatible and fine-tunable) will allow new corneal onlays, inlays and intraocular implants (in the new ERC Advanced Grant Silk Eye).

Organ-on-chips

The Biomedical Applications Group at IMB-CNM-CSIC Organ on a Chip combines 3D microfluidics and sensors integration to simulate organ and tissue specific micro-environments. These systems are applied for toxicological studies and personalized medicine and represent a clear alternative to minimize animal experimentation. An example is the retinal system, which, among others, mimics the blood-brain barrier in the eye.

Personalized nutrition

The relevance of the microbiome and adequate nutrition on health cannot be underemphasized. The Microbiome Ecology, Nutrition and Health Group of IATA-CSIC works on artificial/synthetic microbiota to reduce vulnerability to disease. The understanding of the relation of structural/metabolic compounds produced by the microbiota with biological function can lead to personalized diets and therapeutic strategies of a large range of diseases. This group has coordinated one of the most competitive grants on the human microbiome in Europe (MyNewGut) and is involved in other H2020 EU initiatives.

Vaccines

Vaccines are by far the most powerful strategies for disease prevention. Various well-known groups at the CSIC, are publicly relevant these days for their work on a vaccine against COVID-19. Their work may be highlighted in other sections of the White Book. Here we report the program of Microorganisms for Health and Well-Being Group at CNB-CSIC, who investigates the of Foot-and-mouth disease virus (FMDV), as one of the microorganisms more importantly compromising animal (livestock) health and as an interesting model system for understanding the interactions of a highly variable virus and its natural hosts and the implications of these interactions on disease control. The group works on the development of new FMDV peptide marker vaccines that can induce protective humoral and cellular immune responses in pig and cattle as hosts, as animal models.

2. IMPACT ON BASIC SCIENCE PANORAMA AND POTENTIAL APPLICATIONS

The reported research in New Methods for Prevention and Diagnostics is in many cases at the fore-front of science in Europe, and has enormous potential, not only to advance basic science but also as a generator of technologies with a clinical impact and potential for commercialization, therefore creating an impact also on economy and society.

Identified impact on basic science and technology:

1. Recognized high-risk high-impact research by the European Research Council, with ERC Advanced Grants to Susana Marcos at IO-CSIC(2, Presbyopia and SilkEye), to Ricardo García at CMM (3DNanomech) and to Jose M Benlloch (4D-PET).
2. Many of the groups have been competitive in EU grants (FP6, FP7, Horizon 2020), having been coordinators of large consortia in the area of diagnostics and prevention. For example, the I3M has coordinated several EU consortia (particularly relevant are the MAMMI and MindView) and a FET Open, the IRIS Group of IFIC is part of ENLIGHT (European Network for LIGht ion Hadron Therapy) platform, the VioBio Lab coordinates H2020 ICT Innovation Action IMCUSTOMEYE (with 10 partners) to develop imaging-based biomarkers of corneal disease. The group of IATA CSIC has coordinated MyNewGut and is involved in several other EU projects (MicrobiomeSupport, CIRCLES, miVaO) and co-chairs the EU platform Food for Life.
3. The groups have custom-developed unique competitive technologies including:
   - 3-D Fully Quantitative Anterior Segment Optical Coherence Tomography
   - Eye Wavefront sensing
   - Adaptive Optics Simulators
   - Wearable Simultaneous Vision Visual Simulator
   - Ocular Section Microscopy
   - Multi-meridian Air Puff corneal deformation OCT imaging
   - Improved Ultrasound imaging Methods
   - Full-angle spatial compound of reflectivity imaging
   - Acoustic Radiation Force Impulse (ARFI) imaging
   - Phase Coherence Ultrasound Imaging
   - Ultrasound-based screening for leukocyte screening
   - Atomic Force Microscopy based nanobiomechanics in cells and tissue
   - Single-Molecule Force Spectroscopy based on Atomic Force Microscopy to detect “missing link” conformers in the amyloidogenic cascade and quantifying the conformational polymorphism observed in the amyloidogenic proteins
   - New PET devices
   - Semiconductor positron detectors for β spectrometry
   - Positron traps and moderators to generate high energy resolution

positron beams for scattering experiments
- Models for Positron scattering and to simulate tracks and positron transport in biologically relevant media
- Compton cameras for hadron therapy treatment monitoring
- 3D proton-CT scanner with proton-range verification capabilities
- Nano-radiotracers
- Nanoparticle probes for positive contrast magnetic resonance
- Atomic Force Microscopy based nanobiomechanics in cells and tissue
- Detection methods of glycoproteins isoforms
- Chemical and biological sensors (resistive and magnetic) of breath
- Surface acoustic wave sensors (biosensors)
- Oligonucleotide-based functionalized biosensors
- High-performance devices for advanced biosensing (viral proteins and tumor markers)
- Functional two-dimensional materials (Graphene) chemically linked to RNA or single-stranded DNA oligonucleotids
- Implantable flexible and biocompatible neuroprobes
- Epidermal flexible sensor wearable devices
- Biosensors and lab-on-chip devices for measuring biomarkers in biological fluids
- Machine learning platforms for data processing and functionalized biomarkers
- Corneal and Intraocular Lens implants
- Retina on-a-chip
- Artificial and synthetic microbiotes
- Peptide marker vaccines

4. Some of the groups excel in technology transfer with patent licensing to industry and successful spin-out ventures (i.e. 2EyesVision, Plenoptika, Oncovision, Bruker BioSpin) or are in the process of launching one (i.e. PetInnovation SL). Demonstrated and potential applications include:
   - 3-D Quantitative image-based cataract surgery, being cataract the most frequently performed surgery in the world.
   - Accessible refraction with low-cost, portable wavefront-based autorefractometer (in low resource countries)
   - Selection of contact lens and intraocular lens with SimVis Technology
   - Early detection of keratoconus (a disease affecting 4% of the population)
   - Breast cancer screening through ultrasound

- Early detection of micro-calcification
- Screening of meningitis
- Early diagnostic and disease evaluation at the cellular level of cardiovascular disease and tumors through nanomechanical markers
- Prevention of Post-Traumatic Stress Disorder
- Brain tumor detection
- Heart evaluation
- Tumor limit delineation
- Early in vivo detection of angiogenesis, microcalcifications, neutrophils and oxidised phospholipids.
- Hadron therapy
- Non invasive estimation of the dose distribution in cancer therapies
- Exhaled air detection of diabetes, kidney, liver and respiratory disease.
- Fast, reusable, portable, sensitive, real time, low sample volumes biological sensing
- New disease markers and markers of alteration of immunoglobulins in breast milk
- Neural probing
- Real time and continuous monitoring, and early diagnosis of disease though wearable devices
- Improved detection of thrombin
- Activity measurement of DNA repair enzymes for chemotherapy-induced DNA damage
- Detection of anabolic androgenic steroids
- Detection of biomarkers of inflammation processes
- DNA sequence detection in genetically-modified organisms and bacteria.
- Toxicological studies of drugs for retinal disease on a retina-on-chip
- Impact on development of advanced materials for implants (for ophthalmology, orthopedics, etc), spinecord lesion repairs and foreign body reaction
- Correction of presbyopia and cataract through novel intraocular lenses
- Biocompatible corneal bandages for corneal wound healing
- Corneal onlays, inlays and implants for corneal treatment
- Personalized diet and microbiome-based strategic therapeutic interventions
- Zoonosis and prevention and animal and human virus-borne diseases

3. KEY CHALLENGING POINTS

Although each specific area underpins a series of specific challenges, we summarize here those that we consider common to multiple areas:

1. Challenges in translating results on phantoms or preclinical data to patients.
2. Establishing fruitful collaborations with clinical doctors in the hospital is challenging, particular as CSIC institutes are generally not hosted in hospital campuses.
3. Areas requiring high levels of multi-disciplinarity, which may be challenging to access funding and even to select the appropriate forum for publication. It is an area requiring continuous leaving of the comfort zone.
4. Commercial potential not fully exploited, as it requires an appropriate ecosystem: patent attorneys with specific knowledge, access and knowledge of the specific corporate environment, challenges to license and spin-out creations, and long regulatory processes in medical devices and therapeutic products, requiring costly clinical trials.
5. Added difficulties by the requirement of ethical committees and strict protocols for human studies.
6. Highly experimental area, requiring high levels of funding.
7. Not all institutes (particularly those in physics/engineering/chemistry) have access to biology labs with trained technicians.
8. Need to prove safety and specificity of the diagnostic techniques and therapies.
9. The wide spread of areas make it difficult to identify all possible groups, and sure enough several are missing.
10. Groups perceive as a thread scarce human resources and bureaucratic hurdles that place them in a lower competitive level than their counterparts in other institutions.
11. With so many projects and responsibilities on the Group Leaders' plates it is difficult to secure everyone's attention to creating collaborative programs or a comprehensive and strategic analysis of the area.

CHALLENGE 8 REFERENCES

Albiol , F. Corbi, A. and Albiol, A. (2019). Densitometric radiographic imaging with contour sensors. *IEEE Access* 7:18902-18914.

Aviñó, A., Huertas, C.S., Lechuga, L.M. and Eritja, R. (2016). Sensitive and label-free detection of miRNA-145 by triplex formation. *Analytical and bioanalytical chemistry 408*(3), 885–893.

Barbosa, A.S., Blanco, F., García, G. and Bettega, M.H. (2019). Theoretical study on positron scattering by benzene over a broad energy range. *Physical Review A 100*(4), 042705.

Bueno, R., Marciello, M., Moreno, M. et al. (2019). Versatile Graphene-Based Platform for Robust Nanobiohybrid Interfaces. *ACS Omega* 4(2):3287–3297.

Camacho, J., Parrilla, M. and Fritsch, C. (2009). Phase coherence imaging. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control 56*(5), 958–974

Curatolo, A., Birkenfeld, J. S., Martinez-Enriquez, E. et al. (2020). Multi-meridian corneal imaging of air-puff induced deformation for improved detection of biomechanical abnormalities. *Biomedical optics express 11*(11), 6337–6355.

De Santis, S., Bach, P., Pérez-Cervera, L.et al. (2019). Microstructural white matter alterations in men with alcohol use disorder and rats with excessive alcohol consumption during early abstinence. *JAMA psychiatry 76*(7), 749–758.

De Santis, S., Sommer, W.H. and Canals, S. (2019). *Detecting alcohol-induced brain damage noninvasively using diffusion tensor imaging.*

De Santis, S., Moratal, D. and Canals, S. (2019c). Radiomicrobiomics: Advancing along the gut-brain axis through Big Data analysis. *Neuroscience* 403:145-149.

Dorronsoro, C., Radhakrishnan, A., Alonso-Sanz, J.R., Pascual, D., Velasco-Ocana, M., Perez-Merino, P. and Marcos, S. (2016). Portable simultaneous vision device to simulate multifocal corrections. *Optica 3*(8), 918–924.

Dufrêne, Y. F., Ando, T., Garcia, R.et al. (2017). Imaging modes of atomic force microscopy for application in molecular and cell biology. *Nature nanotechnology 12*(4), 295–307.

Durr, N.J., Dave, S.R., Lage, E., Marcos, S., Thorn, F. and Lim, D. (2014). From unseen to seen: tackling the global burden of uncorrected refractive errors. *Annual review of biomedical engineering 16*, 131–153.

Elvira, L., Durán, C., Higuti, R.T. et al. (2019). Development and Characterization of Medical Phantoms for Ultrasound Imaging Based on Customizable and Mouldable Polyvinyl Alcohol Cryogel–Based Materials and 3-D Printing: Application to High-Frequency Cranial Ultrasonography in Infants. *Ultrasound in medicine & biology 45*(8), 2226–2241.

Farina-Gomez, N., Barrabes, S., Gomez-Lopez, J. E.et al. (2017). Sample preparation of serum to allow capillary electrophoresis analysis of prostate specific antigen isoforms. *Journal of pharmaceutical and biomedical analysis 134*, 220–227.

Fernández-Ramírez, M.C., Hervas, R., Galera-Prat, A., Laurents, D. V. and Carrion-Vazquez, M. (2018). Efficient and simplified nanomechanical analysis of intrinsically disordered proteins. *Nanoscale 10*(35), 16857–16867.

González-Salido, N., Medina, L. and Camacho, J. (2016). Full Angle Spatial Compound of ARFI images for breast cancer detection. *Ultrasonics 71*, 161–171.

Guerrero, C. R., Garcia, P. D. and Garcia, R. (2019). Subsurface imaging of cell organelles by force microscopy. *ACS nano 13*(8), 9629–9637.

Hervas, R., Oroz, J., Galera-Prat, A. et al. (2012). Common features at the start of the neurodegeneration cascade. *PLoS Biol 10*(5), e1001335.

Jiménez, X., Shukla, S.K., Ortega, I. et al. (2016). Quantification of very low concentrations of leukocyte suspensions in vitro by high-frequency ultrasound. *Ultrasound in Medicine and Biology* 42(7):1568-1573.

Le Maout, P., Wojkiewicz, J.L., Redon, N. et al.(2018). Polyaniline nanocomposites based sensor array for breath ammonia analysis. Portable e-nose approach to non-invasive diagnosis of chronic kidney disease. *Sensors and Actuators B: Chemical 274*, 616–626.

Marcos, S., Werner, J.S., Burns, S.A. et al. (2017). Vision science and adaptive optics, the state of the field. *Vision research 132*, 3–33.

Matatagui, D., Fontecha, J. L., Fernández, M. J., Gràcia, I., Cané, C., Santos, J. P. and Horrillo, M. C. (2014). Love-wave sensors combined with microfluidics for fast detection of biological warfare agents. *Sensors 14*(7), 12658–12669.

Oroval, M., Climent, E., Coll, C. et al. (2013). An aptamer-gated silica mesoporous material for thrombin detection. *Chemical Communications 49*(48), 5480–5482.

Oroz, J., Hervás, R. and Carrión-Vázquez, M. (2012). Unequivocal single-molecule force spectroscopy of proteins by AFM using pFS vectors. *Biophysical journal 102*(3), 682–690.

Puerta, A., Díez-Masa, J. C., Martín-Álvarez, P. J.et al. (2011). Study of the capillary electrophoresis profile of intact α-1-acid glycoprotein isoforms as a biomarker of atherothrombosis. *Analyst 136*(4), 816–822.

Robson, R.E., Brunger, M.J., Buckman, S.J., Garcia, G., Petrović, Z.L. and White, R. D. (2015). Positron kinetics in an idealized PET environment. *Scientific reports 5*(1), 1–10.

Solevi, P., Muñoz, E., Solaz, C.et al. (2016). Performance of MACACO Compton telescope for ion-beam therapy monitoring: first test with proton beams. *Physics in Medicine & Biology 61*(14), 5149.

Stevens, D., Babij, T. J., Machacek, J. R.et al. (2018). Positron scattering from pyridine. *The Journal of chemical physics 148*(14), 144308.

Toschi, N., Gisbert, R.A., Passamonti, L., Canals, S. and De Santis S. (2020). Multishell diffusion imaging reveals sex-specific trajectories of early white matter degeneration in normal aging. *Neurobiology of Aging* 86:191-200.

Weaver, J. (2012). Single-molecule technique links structural fluctuations of proteins to brain diseases. *PLoS Biology* 10(5):e1001338.

Williart, A., Muñoz, A., Boscolo, D., Scifoni, E., Krämer, M., and García, G. (2019). Study on Tl-204 simultaneous electron and photon emission spectra and their interaction with gold absorbers. Experimental results and Monte Carlo simulations. *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment 927*, 435–442.

Ytre-Hauge, K. S., Skjerdal, K., Mattingly, J. and Meric, I. (2019). A Monte Carlo feasibility study for neutron based real-time range verification in proton therapy. *Scientific reports 9*(1), 1–9.

A lesson that we have learned from the pandemia caused by coronavirus is that solutions in health require coordinated actions. Beside this and other emerging and re-emerging infectious diseases, millions of Europeans are suffering a plethora of disorders that are currently acquiring epidemic dimensions, including cancer, rare diseases, pain and food allergies, among others. New tools for prevention, diagnosis and treatment need to be urgently designed and implemented using new holistic and multidisciplinary approaches at three different levels (basic research, translational/clinical and public/social levels) and involving researchers, clinicians, industry and all stakeholders in the health system. The CSIC is excellently positioned to lead and coordinate these challenges in Biomedicine and Health.

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