CNB Action Plan 2014-2017

Approved by the Governing Board of the CNB
September 27, 2013

General Information

Origin

Foundation:	Founded in January 1985, inaugurated in July 1992
Founding entity:	Spanish Government, Ministry of Science and Education
First Director:	Michael Parkhouse (1987-1990)

Objective

The National Centre for Biotechnology (*Centro Nacional de Biotecnología*, CNB) was founded by the Spanish Government as a strategic research centre under the umbrella of the Spanish Research Council (*Consejo Superior de Investigaciones Científicas*, CSIC), Spain's largest research institution, with the vision to create a world-leading multidisciplinary research centre that engages in the most relevant areas of red and green Biotechnology.

Description

The Centre was founded in January 1985, under the name "National Centre for Genetic Engineering and Biotechnology" (*Centro Nacional de Ingeniería Genética y Biotecnología*), with the aim to spearhead modern Biotechnology research in Spain. The building in the campus of the *Autónoma* University of Madrid that hosts the CNB today was inaugurated in July 1992 under its actual denomination "National Centre for Biotechnology" (*Centro Nacional de Biotecnología*, CNB.

The mission of the CNB is to generate excellent scientific knowledge and to apply it to solve health, environmental, and agricultural challenges, whilst collaborating with industry and ensuring the transfer of technology. The CNB is committed to the training of highly qualified personnel, offers Biotechnology-oriented counselling and services to the public and private sectors, and creates scientific awareness about modern Biotechnology by disseminating the results of its research and by educating the public and other stakeholders about advances, risks and benefits of contemporary Biotechnology.

Research at the CNB is guided by the ultimate goal to transform scientific advances into innovative tools, products and services that benefit society. The development of vaccines and antibiotics for humans and farm animals, phyto-

and bioremediation strategies, tools to improve plant productivity and their resistance to environmental stress and pathogens, as well as biomarkers and therapeutic targets for chronic inflammatory, autoimmune, infectious and neoplastic diseases are just a few examples to illustrate the problem-oriented focus of the Centre's broad and multidisciplinary approach to tackle real-life challenges with excellent science.

Today, the CNB is one of the largest Spanish research centres, hosting 70 research groups and 20 scientific-technical services. By end of 2012, the Centre employed 347 scientists and 161 technicians and support personnel. The Centre's broad and multidisciplinary research programme covers the areas of Structural Biology, Virology, Microbiology, Plant Genetics, Immunology, Oncology and Systems Biology.

In 2013, the CNB occupies the 49th position in the world, and the 3rd position in Spain, in terms of quality of its scientific production, measured as the percentage of publications in the first quartile of top-ranked scientific journals in their respective field of knowledge (source: SciMago Institutions Ranking 2013).

CNB Directors

Since 2013:	Carmen Castresana
2007-2013:	José María Valpuesta
2003-2007:	José Ramón Naranjo
1992-2003:	Mariano Esteban
1990-1992:	José L. Carrascosa
1987-1990:	Michael Parkhouse

Organisation, Scientific Advisory Board, Departmental Structure, Research Lines

Research Departments

Department of Macromolecular Structures (José María Valpuesta Moralejo)

The activity of this Department focuses on different aspects of the structure of macromolecules, their interactions and the molecular basis of their function. One of the main strengths in this Department is its ample experience and critical mass of research groups in 3D-Electron and X-Ray Microscopy, ranging from Cryoelectron Microscopy to three-dimensional Single Particle Reconstruction, Tomography and correlative methods. Groups focusing on X-Ray Crystallography, Functional Proteomics, Biophysics and Synthetic Molecular Biology complete the Department's ample coverage of key areas in Structural and Functional Biology.

Research groups:

- Functional Proteomics (Juan Pablo Albar Ramírez)
- Three-Dimensional Electron and X-Ray Microscopies: Image Processing Challenges (José María Carazo García)
- Cell-Cell and Virus-Cell Interactions (José María Casasnovas Suelves)
- Structure of Macromolecular Assemblies (José López Carrascosa)
- Viral Molecular Machines (José Ruiz Castón)
- Computational Methods for 3D-Electron Microscopy (José Jesús Fernández Rodríguez)
- Viral Ultrastructure and Macromolecular Aggregates (Jaime Martín-Benito Romero)
- Molecular Biophysics of DNA Repair Nanomachines (Fernando Moreno Herrero)
- Functional Bioinformatics (Alberto Pascual Montano)
- Biophysics and Synthetic Molecular Biology (Víctor Muñoz van den Eynde)
- Cell Structure Lab (Cristina Risco Ortiz)
- Structural and Physical Determinants of Adenovirus Assembly (Carmen San Martín Pastrana)
- Structural Biology of Viral Fibres (Mark Johan Van Raaij)
- Structure and Function of Molecular Chaperones (José María Valpuesta Moralejo)

Department of Immunology and Oncology (Ana Isabel Cuenda Méndez)

Research in this Department addresses various key aspects of innate and adaptive immunity, with special emphasis on characterising the molecular mechanisms that underlie inflammation, the processes that drive tissue-specific tumour development, as well as tumour immunology and the relationships among stem cells, inflammation and cancer. Scientific advances made by this Department contribute to the development of improved approaches for immune response modulation during infection and inflammatory reactions, as well as to the identification of novel targets for the prevention, diagnosis and treatment of cancer.

Research groups:

- Differentiation and Functional Specialisation of Dendritic Cells during Inflammatory, Infectious and Allergic Processes (Carlos Ardavín Castro)
- Interplay of Activation, Apoptosis and Cell Cycle Regulators during Autoimmune T Cell Memory Responses and Inflammation (Dimitrios Balomenos)
- Lymphocytes in Physiological and Pathological Processes: Autoimmune Inflammatory Diseases, Cancer Immunotherapy, and Nanobiomedicine (Domingo Barber Castaño)
- B Cell Dynamics (Yolanda Rodríguez Carrasco)
- Functional Study of PI3K in Survival, Cell Division and Cancer (Ana Clara Carrera Ramírez)
- Role of Stress-Activated Protein Kinase p38MAPK in Human Diseases (Ana Isabel Cuenda Méndez)
- The Role of Epigenetics in Cancer (Mario Fraga Fernández)
- Chemokine-Receptor Interactions in Physiopathological Processes (Leonor Kremer Barón)
- Signalling Networks in Inflammation and Cancer (Santos Mañes Broton)
- Stem Cells and Immunity (Carlos Martínez Alonso)
- Chemokine Receptors: New Targets for Therapeutic Intervention (Mario Mellado García)
- Role of Diacylglycerol Kinases in the Control of Immune Response and Cancer Progression (Isabel Mérida de San Román)
- Function of the c-Myc Proto-Oncogene *in vivo* (Ignacio Moreno de Alborán Vierna)
- Function and Regulation of APRIL, a TNF Protein: Implications in Pathology (Lourdes Planelles Carazo)
- Receptor Ligand Interactions in Immune Responses to Cancer and Viruses (Hugh Thomson Reyburn)

- T Cell Signalling in Autoimmune Diseases and Cancer (Jesús María Salvador Sánchez)
- Biochemical Characterisation of Ligands for the Immune Receptor NKG2D: Implications of Heterogeneity for Pathology and Therapy (María del Mar Valés Gómez)

Department of Cellular and Molecular Biology (Amelia Nieto Martín)

Research in this Department focuses, first, on the structural and functional characterisation of virus and cellular elements involved in the progression of infection and, second, on the molecular basis of mammalian gene expression and control of cell processes in normal and pathological conditions. The first area analyses the role of productive virus-host interactions of human and animal pathogens that are highly relevant for health, while the goal of the second area is the identification and exploitation of relevant diagnostic and therapeutic molecular targets.

Research groups:

- Molecular Bases of Cytoskeletal Reorganisation: Role of Actin Polymerisation in Neuritogenesis, Inflammation and Metastasis (Inés Antón Gutiérrez)
- Replication, Virus-Host Interactions, and Protection in Coronavirus (Luis Enjuanes Sánchez)
- Poxvirus and Vaccines (Mariano Esteban Rodríguez)
- Cellular Factors Involved in Hepatitis C Virus Infection and Pathogenesis (Pablo Gastaminza Landart)
- Biological Noise (Francisco José Iborra Rodríguez)
- Animal Models by Genetic Manipulation (Lluís Montoliu José)
- Functional Analysis of the Transcriptional Repressor Dream (José Ramón Naranjo Orovio)
- Cerebral Cortical Development (Marta Nieto López)
- Mechanisms of Interaction Between the Influenza Virus and the Infected Cell (Amelia Nieto Martín)
- Transcription and Replication of Influenza Virus RNA (Juan Ortín Montón)
- Molecular Characterisation and Epidemiology of Torovirus (Dolores Rodríguez Aguirre)
- Molecular Biology of Birnavirus (José Francisco Rodríguez Aguirre)
- Embryonic Development and Differentiation in Vertebrates (Juan José Sanz Ezquerro)
- Cellular Immunobiology and Microbiology (Esteban Veiga Chacón)

Department of Microbial Biotechnology (José Luis Martínez Menéndez)

This Department integrates research to gain knowledge of key aspects of Microbial Biology with environmental, clinical or biotechnological relevance. The department hosts ten groups that focus on complementary aspects of Microbial Biology with approaches that include Molecular Genetics, Genomics, Proteomics and Metagenomics. The subjects studied include environmental microbiology, microbial responses to hostile environments, microbial pathogens, microbial engineering, microbial resistance to antibiotics and search for new antimicrobials.

Research groups:

- Genetic Stability (Juan Carlos Alonso Navarro)
- Recombination-Dependent DNA Replication (Silvia Ayora Hirsch)
- Stress and Bacterial Evolution (Jesús Blázquez Gómez)
- Cell Cycle, DNA Replication and Genome Stability in Eukaryotes (José Arturo Calzada García)
- Protein Secretion and Antibody Expression (Luis Ángel Fernández Herrero)
- Intracellular Bacterial Pathogens (Francisco García del Portillo)
- Opportunistic Pathogens (José Luis Martínez Menéndez)
- Heterologous Gene Expression and Secretion in Gram-Positive Bacteria of Industrial Application (Rafael Pérez Mellado)
- Regulation of the Metabolism of Hydrocarbons in Bacteria (Fernando Rojo de Castro)
- Genetic Control of the Cell Cycle (Miguel Vicente Muñoz)

Department of Plant Molecular Genetics (Juan Antonio García Álvarez)

Research in this Department focuses on signalling pathways involved in the main growth and adaptive responses of plants to environmental changes and pathogenic diseases. Besides the intrinsic fundamental interest in understanding key biological processes in plants, the ultimate goal is to develop new tools and methods to improve crop production and quality, selection of new varieties more resistant to pathogens or their modification to reduce fertiliser needs. Biotechnological applications such as the use of plants as biopharmaceutical factories or as tools to fight environmental problems arising from spillages and the accumulation of toxic substances are also being studied.

Research groups:

- Genetic and Molecular Basis of Naturally-Occurring Variation in Plant Development (Carlos Alonso Blanco)
- Plant Immunity Strategies Against Microbial Pathogen Infection (Carmen Castresana Fernández)
- Genetic Analysis of Axillary Meristem Development (Pilar Cubas Domínguez)
- Plant-Pathogen Interaction in Viral Infections (Juan Antonio García Álvarez & Carmen Simón Mateo)
- Molecular Mechanisms Underlying Root Architecture and Arsenic Phytoremediation (Antonio de Leyva Tejada)
- Regulation of Gene Activity in Plants: The Phosphate Starvation Rescue System (Javier Paz-Ares Rodríguez)
- Hormonal Control of Light Signalling (Salomé Prat Monguió)
- Intracellular Trafficking in Plants (Enrique Rojo de la Viesca)
- Role of Ubiquitin in The Control of Plant Growth and Stress Tolerance (Vicente Rubio Muñoz)
- Signalling Networks in Plant Development and Defence Responses (José Juan Sánchez Serrano)
- The Jasmonate Signalling Pathway in *Arabidopsis* (Roberto Solano Tavira)

Research Programmes

Systems Biology Programme (Víctor de Lorenzo Prieto)

Research efforts in this still relatively young Research Programme, created in late 2008 in order to spearhead the implementation of Systems Biology approaches, attempt to understand how bacteria that inhabit natural niches sense and process multiple environmental signals into distinct transcriptional and post-transcriptional responses, both at the level of single cells and as a community. The biotechnological side of this biological question is the possibility of programming bacteria for deliberate environmental release, aimed at biodegradation of toxic pollutants or as biosensors to monitor the presence of given chemicals.

Research groups:

- Molecular Environmental Microbiology (Víctor de Lorenzo Prieto)
- Computational Systems Biology (Florencio Pazos Cabaleiro)
- Logic of Genomic Systems (Juan Fernando Poyatos Adeva)
- Microbial Community Modelling (Javier Tamames de la Huerta)

Associated Units

Nanobiotechnoloy Unit (José López Carrascosa)

Joint Nanobiotechnology research platform participated by the CNB and the IMDEA Nanoscience Foundation.

Research Support

- Scientific Management (Peter Klatt Brückl)
- Technology Transfer (Ana Sanz Herrero)
- Outreach and Communication (Alfonso Mora Corral)

Scientific Services

- Electron Microscopy (Cristina Patiño Martín)
- Confocal Microscopy (Sylvia Gutiérrez Erlandsson)
- Macromolecular X-Ray Crystallography (César Santiago Hernández)
- Proteomics (Juan Pablo Albar Ramírez)
- Protein Tools (Leonor Kremer Barón)
- Genomics (José Manuel Franco Zorrilla)
- Flow Cytometry (María del Carmen Moreno-Ortiz Navarro)
- Greenhouse (Tomás Heras Gamo)
- *In Vitro* Plant Culture (Raquel Piqueras Martín)
- Animal Facility (Angel Naranjo Pino)
- Mouse Embryo Cryopreservation (Lluís Montoliu José)
- Transgenesis (María Belén Pintado Sanjuanbenito)
- Histology (Lluís Montoliu José)
- Bioinformatics Initiative (Alberto Pascual Montano)
    - Computational Genomics (Juan Carlos Oliveros Collazos)
    - Sequence Analysis and Structure Prediction (Mónica Chagoyen Quiles)
    - Scientific Computing (José Ramón Valverde Carrillo)
    - Computational Proteomics (Alberto Medina Auñon)
    - Functional Analysis (Alberto Pascual Montano)
    - Statistical Analysis (Carlos Óscar Sánchez Sorzano)
- Radiation Protection and Biological Safety (Fernando Usera Mena)

Technical Support

- Library (María Dolores Aparicio Trujillo)
- Information Technologies (Sonia de Diego Atance)
- Instrumentation (Ismael Gómez López)
- Workshop (Daniel Pastora Muñoz)
- Washing and Sterilisation (Rosa María Bravo Igual)
- Maintenance (Antonio Dueñas Novillo)
- General Services (Gabriel Sánchez de Lamadrid Herranz)
- Security (Sócrates Gutiérrez Monreal)

Administration

- Human Resources (Marina Hernando Bellido)
- Project Management (Soraya Olmedilla María)
- Economic Management (Mariano Muñoz Jiménez)
- Purchasing and Supplies (Ramon Serrano Coronado)

Governance

The CNB is headed by an executive **Director** (Carmen Castresana Fernández) and two **Vice-Directors** (Isabel Mérida de San Román, Fernando Rojo de Castro). The administration of the CNB, including technical and administrative support units, are coordinated by the Centre's **General Manager** (Miguel Anchuelo Calzada).

The Director and Vice-Directors are elected every four years by the Centre's scientists in the assembly of the **General Board**, constituted by the academic staff (PhDs), presided by the Director, and with the General Manager as Secretary.

The CNB has a **Governing Board**, headed by the CNB Director and Vice-Directors, that includes the Heads of the Centre's six research areas, four representatives of the centre's personnel and the General Manager. The Board meets monthly to plan, discuss, implement and inform about decisions taken by the Centre's Direction.

An external **Scientific Advisory Board** closely monitors the Centre's scientific activities through periodic evaluations and acts as permanent advisory organ to the Director of the CNB. The board is composed by Anna Tramontano (Professor of Biochemistry at the University of Rome *La Sapienza*, Italy), Anne Ridley (Professor of Cell Biology at King's College London, United Kingdom), Inder Verma (Professor of Genetics at the Salk Institute for Biological Studies, La Jolla, CA, USA), Juan Luis Ramos (Professor of Molecular Biology at the CSIC research centre *Estación Experimental del Zaidín*, Granada, Spain), Maarten Koorneef (Director of the Plant Breeding & Genetics Department at the Max Planck Institute for Plant Breeding Research, Cologne, Germany) and Wolfgang Baumeister (Director of the Molecular Structural Biology Department at the Max Planck Institute for Biochemistry, Martinsried, Germany).

Scientific Services

Electron Microscopy (Cristina Patiño Martín)

The Electron Microscopy Service offers a variety of equipment and techniques for the preparation, processing and analysis of biological samples (cell and bacterial cultures, cell fractions, proteins, viruses, animal and plant tissues) by Transmission Electron Microscopy. The technical staff provides support to users in the correct use of equipment and methodologies. The Service offers regular training in the techniques and methods available. Services further include sample preparation, if required, as well as image acquisition, and support for data interpretation. Techniques offered include chemical fixation and inclusion in epoxy and acrylic resins, cryofixation (plunge freezing, high pressure freezing), freeze substitution and inclusion in low temperature resins, ultramicrotomy, negative staining, immunonegative staining, immunelabelling, *in situ* hybridisation, conventional transmission electron and low-dose electron microscopy.

Activity (2010-2012)
Service users: 192
Trained users: 107

Economic impact (2010-2012)
Internal users: 73.1 k€
Other CSIC centres: 2.7 k€
Universities: 4.2 k€
Enterprises: 1.2 k€
TOTAL: 81.2 k€

Confocal Microscopy (Sylvia Gutiérrez Erlandsson)

Confocal Microscopy imaging techniques use lasers and electronic systems of digital image capture to provide optical sections of the studied material. The presence of fluorescent markers in the sample allows location of cell components in single sections and various experimental approaches, involving single or multiple fluorescent labelling in fixed cells and tissues. The Confocal Microscopy Service provides infrastructure for fluorescence, confocal laser scanning microscopy and image processing tools, covering most light microscopy applications. The equipment and services are available to all CNB personnel as well as to researchers from the public and private sectors. The technical staff offers assistance and training about equipment use, available methods, and for

image processing, quantification and analysis. Aliquots of secondary antibodies and probes with broad use in fluorescence microscopy applications are also provided.

The facility's equipment includes:

- Confocal multispectral Leica TCS SP5 system. Laser lines: 405, 458, 476, 488, 514, 561, 594 and 633 nm. Incubation system for *in vivo* studies
- BioRad Radiance 2100 confocal system. Laser lines: 457, 476, 488, 514, 543 and 637 nm
- Fluorescence microscope Leica DMI6000B with incubation system for *in vivo* studies and OrcaR2 monochrome digital camera for image detection
- Two epifluorescence microscopes (Leica DMRXA and Zeiss Axiophot) with colour digital cameras and one Leica stereomicroscope
- The unit also provides offline computer workstations for fluorescence and confocal image processing and analysis (LAS AF, MetaMorph, Image J, Laser Pix, Huygens, Imaris)
- Auxiliary equipment: CO2 incubator, centrifuge, laminar flow chamber, freezer

Laser scanning confocal microscopy applications:

- Multichannel confocal imaging + transmission imaging of living cells or fixed samples (2D, 3D, 4D imaging)
- High speed confocal microscopy
- Multidimensional *in vivo* time-lapse experiments
- FRET, FRAP, photoactivation, photoswitching, lambda scan, calcium imaging
- Subcellular co-localisation studies

Widefield applications:

- Multichannel fluorescence imaging + transmission imaging (BF, DIC, phase contrast)
- Multidimensional *in vivo* time lapse experiments (wound healing, infection etc.)
- Tile scan imaging

<u>Activity (2010-2012)</u>
Service users: 44
Trained users: 40

<u>Economic impact (2010-2012)</u>
Internal users: 59.8 k€
Other CSIC centres: 1.7 k€
Universities: 0.6 k€
TOTAL: 62.1 k€

Macromolecular X-ray Crystallography (César Santiago Hernández)

Protein X-Ray Crystallography is a high-resolution technique to study protein structure at the atomic level. This method provides a detailed view of protein function, ligand and protein interactions, supra-molecular organisation and mutants related to human diseases. Great improvements both in crystallisation techniques and in software for structure resolution and refinement have been achieved in the last decade, increasing the chances of solving a macromolecule structure.

Services:

- Advice and supervision on protein production, from cloning to expression in bacterial, yeast and eukaryotic systems
- Support and training on protein purification to obtain crystal-grade protein for crystallisation
- Automated macromolecular crystallisation
- Crystallisation condition optimisation, applying standard and in-house techniques
- Crystal mounting, access to synchrotron beam time and X-ray diffraction data collection
- Data processing and structure resolution and analysis

Equipment:

- Three temperature-controlled crystallisation rooms
- Genesis RSP 150 workstation (Tecan Trading AG) nanodispenser robot
- Rigaku Desktop Minstrel system for automated crystallisation plate visualisation
- CrystalTrak database suite for crystallisation screening and improvement of positive trials

Activity (2010-2012)
Service users: 19
Trained users: 23

Economic impact (2010-2012)
Internal users: 3.0 k€
TOTAL: 3.0 k€

Proteomics (Juan Pablo Albar Ramírez)

The CNB Proteomics Facility maintains a technological platform suitable for large-scale protein identification and characterisation, offering its services to the CNB scientific community as well as to external researchers. Massive protein identification and characterisation is performed by multidimensional nano-HPLC chromatography coupled to a nano-electrospray ion trap mass spectrometer (MS), to a TripleQ-TOF MS, or to a MALDI TOF/TOF MS (LC-MS/MS). Differential proteomics (quantitative proteomics) is done by analysis of fluorescent-labelled samples and differential 2D-electrophoresis (2D-DIGE), as well as by stable isotope labelling (ICPL, SILAC, iTRAQ) in combination with LC-MS/MS. SELDI-ToF MS (surface enhanced laser desorption-ionisation-time of flight mass spectrometry) is used to obtain protein expression profiles. The Facility further offers targeted and quantitative protein analysis by selected/multiple reaction monitoring (S/MRM-MS). Prolamin detection and characterisation by ELISA, quantitative PCR and mass spectrometry form also part of the Facility's analysis portfolio. For educational purposes, the Facility staff organises practical courses on topics such as quantitative proteomics and bioinformatics. The Head of the CNB Proteomics facility, Juan Pablo Albar, is also the General Coordinator of ProteoRed-ISCIII (*Plataforma en Red de Proteómica-Carlos III*).

The Facility provides the following services:

- Two-dimensional gel electrophoresis/differential proteomics (2D-DIGE)
- Protein identification and characterisation by MALDI-TOF/ TOF, TripleQ-TOF, ProteinChip/SELDI-TOF and ESI MS/MS mass spectrometry
- Selected/multiple reaction monitoring (S/MRM-MS)
- Protein profiling, purification and biomarker determination by SELDI-TOF MS
- Identification and characterisation of post-translational modifications
- Peptide synthesis and membrane-bound peptide array design
- Gluten analysis by ELISA, PCR and mass spectrometry

<u>Activity (2010-2012)</u>
Service users: 136
Trained users: 12

<u>Economic impact (2010-2012)</u>
Internal users: 104.2 k€
Other CSIC centres: 157.2 k€
Universities: 140.0 k€
Enterprises: 81.4 k€
TOTAL: 482.8 k€

Protein Tools (Leonor Kremer Barón)

The Protein Tools Unit focuses on the design, production and characterisation of custom monoclonal antibodies (mAb), immune response studies, development of specific immunoassays, protein labelling and biomolecular interactions analysis. A wide panel of mAbs against different types of antigens has been developed, including fluorescent proteins (GFP), blood proteins (coagulation Factor V), neurodegenerative disease-related proteins (TAU, beta amyloid peptides), membrane raft proteins (MYADM), chemokine receptors (CCR9), FERM-containing proteins (Protein 4.1R) and nuclear proteins (Dido). The facility has a surface plasmon resonance biosensor for the characterisation of biomolecular interactions in real time and determination of kinetic and affinity constants. This technique is applied to a wide range of samples such as proteins, antibodies, nucleic acids, carbohydrates, lipids, low molecular weight compounds, liposomes and viruses. Research tools and services are provided to scientists from the CNB, other CSIC institutes, universities, public research organisations and private companies. The Facility offers expertise in Immunobiology and Immunochemistry, technical assistance, data analysis, training in specific techniques, implementation of new methodologies and advice. In addition, the Facility organises theoretical and practical training courses.

Equipment:

- Biological safety cabinets (Nuaire 437-400E)
- Centrifuges and microfuges (Hettich)
- Inverted fluorescence microscope (Zeiss Axiovert 40 CFL)
- CO2 incubators (Thermo Steri-Cult)
- ÄKTAprime plus chromatography system (GE Healthcare)
- SPR Biacore 3000 (GE Healthcare)
- EnVision 2104 Multilabel Reader (Perkin Elmer)
- Thermal cycler (Eppendorf AG)
- Microplate reader (Bio-Rad 680)
- Protein gel electrophoresis and Western blotting systems (Mini- PROTEAN 3 and Mini Trans-blot cells)
- Electrophoresis power supply units (Bio-Rad PowerPac Basic and Universal)

<u>Activity (2010-2012)</u>
Service users: 32
Trained users: 46

Economic impact (2010-2012)
Internal users: 54.0 k€
Other CSIC centres: 13.2 k€
Universities: 6.6 k€
Enterprises: 3.1 k€
TOTAL: 76.9 k€

Genomics (José Manuel Franco Zorrilla)

The Genomics Unit at the CNB focuses on gene expression analysis using microarrays (or DNA "chips"). This technology allows the study of gene expression from different biological samples, interrogating the activity of thousands of genes or complete genomes at once, which will help to elucidate the genetic basis of biological processes under study. The Unit routinely hybridises and analyses one- and two-channel microarrays. The currently supported platforms include Affymetrix, Agilent and custom microarrays.

Services are offered to CNB and external researchers; they include microarray printing, RNA integrity analysis and microarray hybridisations. The Unit also provides statistical analysis and bioinformatics support. Raw data are statistically analysed using state-of-the-art algorithms and filtered results are supplied to customers in an easy-to-use, web-based tool developed in the Unit. The Unit offers advice and support in the use of several bioinformatics tools for functional analysis of genes and genomes, helping customers with the biological interpretation of the results. The Unit also offers the possibility of validating gene expression data by real time qPCR analysis. In addition the Unit offers the TILLer Service to search for EMS-induced mutants in the model plant *Arabidopsis thaliana*; TILLer is available through the CNB web page (www.cnb.csic.es/~tiller) or through the international *Arabidopsis* web page (www. Arabidopsis.org).

Through the Genomics Unit, the CNB participates in the CSIC-PCM Ultrasequencing Platform, physically located at the Madrid Science Park (*Parque Científico de Madrid*). This Platform can perform massive sequencing experiments using Genome Analyzer or Genome FLX systems, and allows the sequencing of complete genomes, transcriptomes, small RNAs or DNA/RNA-protein interactions. Research projects are constantly being developed by the Genomics Unit to implement new services and technologies for customers. These include microarray-based technologies, such as a new DNA chip for studying DNA-protein interactions, analysis of the translatome, and new strategies for analysis of the miRNA-guided degradome.

Equipment:

- Complete Affymetrix platform, including fluidics station, hybridisation oven and scanner (3000 7G)
- High-resolution scanner for 1- and 2-colour microarrays (Agilent Microarray Scanner)
- Hybridisation system for NimbleGen microrarrays
- Microarray spotter MicroGrid II (Genomic Solutions)
- Bioanalyser 2100 (Agilent) for analysis of RNA/DNA sample integrity
- Automated liquid-handling workstation (Biomek 2000, Beckman Coulter)
- Laser scanner for 2-colour microarrays (Axon 4000B)
- 7900HT Fast Real-Time PCR System (Applied Biosystems)

Activity (2010-2012)
Service users: 97
Trained users: 8

Economic impact (2010-2012)
Internal users: 245.0 k€
Other CSIC centres: 243.2 k€
Universities: 202.0 k€
TOTAL: 690.2 k€

Flow Cytometry (María del Carmen Moreno-Ortiz Navarro)

The Facility provides scientific and technological support to CNB research groups by offering:

- Training in and advice on the principles and applications of analytical flow cytometry, to obtain maximum advantage
- Development and optimisation of applications that incorporate new technologies and reagents
- Quantification of secreted cytokines by multiplexed assays
- Results analysis using specialised software
- Cell isolation by cell sorting (sorting of cell populations including cell suspensions derived from any animal organ and from cell lines)

The Facility's equipment includes:

- BD FACSCalibur Analyser: 4 colours, 2 laser excitation (488 nm, 633 nm)
- Beckman Coulter EPICS XL-MCL Analyser: 4 colours, 1 laser excitation (488 nm)
- Beckman Coulter CYTOMICS FC 500 Analyser: 5 colours, 2 laser excitation (488 nm, 633 nm)

- Beckman Coulter CYTOMICS FC 500 Analyser: 5 colours, 1 laser excitation (488 nm)
- BD LSRII Analyser: 8 colours, 3 laser excitation (488 nm, 633 nm, 405 nm)
- Beckman Coulter GALLIOS Analyser: 10 colours, 3 laser excitation (488 nm, 633 nm and 405 nm)
- Luminex 100 IS Multiparametric Analyser: A system that can be used to quantify multiple cytokines (up to 100) or any other soluble molecule from a single sample
- Recently, the unit acquired a Cell Sorter Beckman Coulter Moflow XDP: 10 colours, 3 laser excitation (488 nm, 633 nm, 405 nm)
- The facility also provides the computer science system to analyse the results obtained: 2 PC platforms running specialised software packages (WindMDI , CXP, MultiTime, MultiCycle, DIVA, Flowjo, Summit, Kaluza)

Activity (2010-2012)
Service users: 68
Trained users: 100

Economic impact (2010-2012)
Internal users: 286.0 k€
Other CSIC centres: 20.9 k€
Universities: 6.0 k€
Enterprises: 3.7 k€
TOTAL: 316.6 k€

Greenhouse (Tomás Heras Gamo)

Infrastructure:

- Standard greenhouse with 8 cabinets (total growth surface: 180 square meters)
- P2 safety level greenhouse with 4 cabinets (total growth surface: 83 square meters)
- 18 climate chambers

Services:

- Growth and propagation of plants under controlled environmental conditions
- Growth and propagation of mutant and transgenic lines under controlled environmental conditions
- Identification, selection and phenotypic analysis of mutant and transgenic plants

Activity (2010-2012)
Service users: 13
Trained users: 3

Economic impact (2010-2012)
Internal users: 47.4 k€
TOTAL: 47.4 k€

***In vitro* Culture and Transgenic Plants** (Raquel Piqueras Martín)

Services:

- Preparation of media
- Sterilisation of seeds and seed sowing in plates
- Maintenance of plants, plant cell cultures and plant callus
- Explant propagation
- Selection of *Arabidopsis* transformants
- Transformation of *Nicotiana* spp., *Solanum* spp., *Lycopersicum* spp., *Oryza* spp.
- Induction of *Arabidopsis* callus, and induction of plant shoots and plant roots from callus
- Storage of wild seeds of the species most frequently used at the CNB
- Mesophyll protoplast preparation

Activity (2010-2012)
Service users: 12
Trained users: 4

Economic impact (2010-2012)
Internal users: 84.0 k€
TOTAL: 84.0 k€

Animal Facility (Angel Naranjo Pino)

The Animal Facility is an area dedicated to the production and maintenance of experimental animals, supporting research, essential techniques, and legal support for this duty. The Facility provides a controlled environment for the animals, with periodic control of diet, water, temperature, air, housing and husbandry conditions. Most of the experimentation is carried out with genetically modified mice. The Animal Facility is separated into several areas: quarantine, conventional, and specific pathogen-free (SPF), depending on the microbiological status of the animals; special housing conditions for conventional, genetically

modified and immunodeficient animals are provided depending on the experimental objectives. At the same time, a totally isolated biosafety area is dedicated to *in vivo* experiments with biological agents.

The Animal Facility staff provides service to researchers for obtaining commercial lines and strains of animals, shipping animals for collaboration with other institutes, as well as for the maintenance, breeding, and generation of transgenic, knock-out and knock-in animals. These services allow control of the microbiological and genetic quality of the animals used in experimentation. The animal facility staff provides services for various techniques used in mouse research models. Veterinary staff gives research assistance in surgical techniques, selection of animal models, animal health surveillance, laboratory animal care, and animal wellbeing. The goal of the Facility is to achieve research excellence following the 3R principles: reduction, refinement, and replacement of animal experiments.

Activity (2010-2012)
Service users: 96
Trained users: 18

Economic impact (2010-2012)
Internal users: 1,182 k€
Other CSIC centres: 6.3 k€
Enterprises: 1.7 k€
TOTAL: 1,190 k€

Mouse Embryo Cryopreservation (Lluís Montoliu José)

The Mouse Embryo Cryopreservation Facility offers the possibility of cryopreserving transgenic and mutant mouse lines as frozen embryos and/or sperm. The Facility also offers thawing of frozen mouse sperm and/or embryos and revitalisation of the cryopreserved mouse line. The cryopreservation of mouse lines is a highly recommended procedure to preserve animal models used in Biology, Biomedicine and Biotechnology laboratories for long periods of time, safely and stably, without the need to maintain lines alive. This saves space and money and optimises the use of experimental animals, complying with current legislation on animal welfare.

The Facility offers a variety of services and the latest methods in the field, including freezing 8-cell mouse embryos, freezing IVF-derived 2-cell mouse embryos, thawing mouse embryos and associated embryo transfer procedures to suitable pseudopregnant females for the revitalisation of mouse lines, freezing

mouse sperm, thawing mouse sperm and *in vitro* fertilisation (IVF), storage of cryopreserved mouse embryos or sperm in liquid nitrogen.

The CNB also hosts the Spanish node of the European EMMA project (European Mouse Mutant Archive, www.emmanet.org), coordinated by Lluís Montoliu. The objective is the cryopreservation, organised archiving and coordinated distribution of mouse lines of interest to the biomedical research community. The EMMA project, EMMAservice (2009-2012), funded by the European Commission (FP7), has been extended for four additional years under the new FP7 Project Infrafrontier-I3 (2013-2016), approved by the European Commission in 2012.

In 2012, the CSIC and the Spanish National Cancer Research Centre (CNIO) signed an agreement to archive and distribute mutant mice of interest in biomedical research that have been generated by CNIO investigators through the EMMA project and its Spanish node at the CNB. Also in 2012, the CSIC and the University of Kumamoto signed a cooperation agreement to promote exchange of knowledge, personnel and information on mouse embryo and sperm cryopreservation and archiving activities undertaken by the Spanish EMMA node at the CNB and the CARD archive, coordinated in Japan by Prof. Naomi Nakagata. The CNB Mouse Embryo Cryopreservation Facility is integrated within the INNOTEK Scientific-Technological Platform as part of the UAM+CSIC International Campus of Excellence.

Activity (2010-2012)
Service users: 70
Trained users: 9

Economic impact (2010-2012)
Internal users: 28.2 k€
Other CSIC centres: 17.2 k€
Universities: 14.0 k€
Enterprises: 37.0 k€
TOTAL: 96.4 k€

Transgenesis (María Belén Pintado Sanjuanbenito)

The CNB-CBMSO Transgenics Unit is jointly operated by the CNB and the CBMSO as part of the UAM+CSIC International Campus of Excellence and provides support to researchers in the creation, establishment and interchange of genetically modified mouse models. The Unit offers technical and scientific advice on the best strategy to achieve the desired model, either by additive transgenesis or targeted mutagenesis (knock-out and knock-in). The Unit also

facilitates the incorporation of those models already available from international consortia or as a result of scientific interchange when the health status of the original colony does not meet the requirements of the receiving centres. In addition, support is provided for breeding schemes to ensure the most suitable genetic background.

Services:

- Advice in the design of target vectors or constructs for microinjection
- Pronuclear microinjection of plasmid, BAC or YAC DNA
- Vector electroporation in R1 or G4 ES cell lines
- Zinc finger nuclease injection
- International consortia ES cell handling
- ES cell injection or aggregation to generate chimaeras
- Embryo rederivation through IVF or embryo transfer
- DNA purification and founder identification by PCR on request
- Reproductive biotechnology to solve breeding problems of genetically modified mice
- Support in the generation, establishment and management of genetically altered mouse lines
- These activities are combined with training and education on demand, and applied research to develop and refine reproductive technologies to enhance transgenic production efficiency or colony management.

Specialised equipment:

- Two microinjection systems with hydraulic micromanipulation system and Eppendorf femtojet injector
- One electric microinjection system with piezo drill
- Dissecting microscopes
- Microforge and pipette puller
- Thermocycler and electrophoresis equipment
- Fully equipped laboratory for ES cell handling

<u>Activity (2010-2012)</u>
Service users: 25
Trained users: 0

<u>Economic impact (2010-2012)</u>
Internal users: 81.0 k€
Other CSIC centres: 37.0 k€
Universities: 32.4 k€
TOTAL: 150.4 k€

Histology (Lluís Montoliu José)

The Histology Facility offers methods for the histological analysis of animal and plant biological samples. Available methods include the preparation of paraffin/wax blocks and plastic (Historesin) for obtaining histological sections with the automated microtome, and the preparation of blocks for obtaining sections from frozen tissue with the cryostat. Sections can be counterstained or assigned for later analysis by immunohistochemistry. The Facility is equipped with a cryostat, two automated microtomes, a tissue processor carrousel, a paraffin/wax embedding machine, two water baths, a stereoscope, an oven, and additional small equipment to process all kinds of tissue samples. The Facility's expertise is reflected by the large variety of tissue samples and species processed (www.cnb.csic.es/~histocnb/tabla.html).

Since 2009, the CNB Histology Facility is associated with the IIB-UAM/CSIC Histology Facility (www.iib.uam.es/servicios/patexperimen/intro.es.html). Both centres merged the operations of their Facilities under the coordination of the CNB Histology Facility, offering CNB and IIB researchers increased processing capacity of histological samples. The CNB Histology Facility is integrated within the INNOTEK Scientific-Technological Platform as part of the UAM+CSIC International Campus of Excellence.

Activity (2010-2012)
Service users: 120
Trained users: 5

Economic impact (2010-2012)
Internal users: 23.6 k€
Other CSIC centres: 11.8 k€
Universities: 26.9 k€
Enterprises: 3.5 k€
TOTAL: 65.8 k€

Computational Genomics (Juan Carlos Oliveros Collazos; service operative since September 2012)

Current advances in genomics-related technologies such as DNA microarrays and, more recently, ultrasequencing methods allow Life Science researchers to gather huge amounts of genome-wide data in little time and at a relatively low cost. Transforming these (raw) data into results, and these results into relevant biological conclusions, requires integrating specific biology and informatics skills, and the use of special software and hardware. The CNB's Computational

Genomics Service provides researchers with global Bioinformatics support for the analysis, visualisation, and interpretation of data obtained in their genomics-related projects.

Services include among others:

- Assistance in experimental design for ultrasequencing and DNA microarray projects
- Biostatistical support for the correct interpretation of genomics- related results
- Genomic data viewer development and maintenance
- Development of final user interfaces for third-party bioinformatics tools
- Organisation of periodic courses and tutorials on bioinformatics and genomics

In short, the Computational Genomics Service aims to fill the gap between the complex outcome of the many powerful biostatistical methods available and the final user's needs that require placing these heterogeneous results in the context of their research projects.

Activity (September – December 2012)
Service users: 23
Trained users: 1

Economic impact (September – December 2012)
Internal users: 0.6 k€
Other CSIC centres: 0.5 k€
TOTAL: 1.1 k€

Sequence Analysis and Structure Prediction (Mónica Chagoyen Quiles)

Sequence analysis and protein structure prediction methods can explain, simplify and further guide experimental work. The Service specialises in *ad hoc* analysis of protein sequences to solve specific problems or questions. The most frequent activities of the service are to:

- Predict protein structure
- Search for homologous proteins
- Generate multiple sequence alignments
- Produce structural organisation drafts
- Study relevant residues for protein structure/function
- Extract sequence features from full proteomes

Additional services include:

- DNA/RNA motif discovery
- Consultancy in the use of sequence-based methods
- High-quality protein sequence/structure images for publication

In collaboration with other CNB services, the Service also organises periodic courses on Bioinformatics approaches for sequence analysis and protein structure prediction. The service is offered to the CNB-CSIC as well as to other academic institutions and private organisations.

Activity (2010-2012)
Service users: 41
Trained users: 78

Economic impact (2010-2012)
TOTAL: 0 k€

Scientific Computing (José Ramón Valverde Carrillo)

The Scientific Computing Service actively engages in international initiatives, such as EMBnet and SOIBIO (the Iberoamerican Society for Bioinformatics), and research collaborations to address scientific needs. The node delivers advanced Structural Biology services encompassing molecular modelling, drug-receptor interactions and Computational Quantum Chemistry. These tools are being applied in red (Health) Biotechnology to understand the effects of potent mutagens (such as 8-oxo-GTP), the functional impact of point mutations, and to analyse the interaction and effects of novel drugs for agricultural plagues. Simultaneously, the service provides data analysis services for Next Generation Sequencing Metagenomic data, applied in both red Biotechnology (antibiotic resistance and opportunistic organisms) and green Biotechnology (effects of herbicides on the rhizosphere).

Over the years, the Service has built a large expertise on Bioinformatics that is disseminated through a dynamic and continuously adapting program of international courses on topics including Biostatistics, Phylogenetics, Molecular Simulations, Metagenomics and Computer Programming. Concerned with growing analytical costs, FreeBIT, the Iberoamerican Network on Free Software for Life and Health, (CYTED 510RT0391) is being coordinated from the CNB to promote the adoption and development of free software in the region, with estimated savings for participating countries of many hundreds of thousands of Euros. Participation in SEQAHEAD (COST action BM1006) enables the Service to

convey users' needs to the broader Bioinformatics community and bridge the gap between wet lab and software developers.

Activity (2010-2012)
Service users: 50
Trained users: 200

Economic impact (2010-2012)
TOTAL: 0 k€

Computational Proteomics (Alberto Medina Auñón)

The Computational Proteomics Service has as main roles the interpretation, validation and reporting of data derived from proteomics experiments. The Service forms part of the CNB Proteomics Facility.

Services:

- Support of dedicated computing infrastructures
- Mass spectrometry data (MS) validation: obtain identified proteins/peptides by crossing results from different search engines
- Proteins/peptides validation: MS and Mass Spectrometry Informatics (MSI) statistics support for proteomics experiment results
- Protein cross-referencing: Extract homologous protein ids among different protein databases
- Protein annotations: Extract the biological information regarding a set of identified proteins
- Experiment reporting
- Generation of MS and MSI standard reports (PRIDE and MIAPE) for public deposition (required by specialized journals)
- Generation HUPO-PSI XML files from MIAPE reports for MS, MSI and GE experiments
- Data visualization using standard-based third party tools
- Proteomics web sites parsing: Extracting regular data from proteomics-based web sites
- Tutorials and training courses regarding the listed items

Activity (2010-2012)
Service users: 50
Trained users: 200

Economic impact (2010-2012)
TOTAL: 0 k€

Radiation Protection and Biosafety (Fernando Usera Mena)

Services:

- Risk assessment
- Acquisition of security materials
- Design of laboratories and facilities
- Acquisition and management of radioisotopes
- Editing health and safety manuals
- Processing of legal documentation
- Training and information in chemical, biological and radiation for staff
- Classification and signposting in laboratories
- Control of compliance with health and safety norms
- Control and management of staff medical and dosimetry surveillance; records maintenance
- Intervention in accidents and emergencies
- Control of production and processing of hazardous waste
- Internal transport and storage of waste for transfer to authorised or controlled disposal

The Service supervises hazardous operations in CNB laboratories and directly manages the gamma irradiator and the central radioisotopes laboratory, equipped with:

- 2 safety cabinets for radioisotopes
- CO2 incubator
- Biosafety cabinet
- Ultracentrifuge, centrifuges and microcentrifuge
- Speed vac
- Hybridisation oven

The Service manages a level 3 biological containment (P3) laboratory, consisting of three sub-laboratories for *in vitro* culture with all necessary equipment for safe handling of Risk Group 3 biological agents and contained use of genetically modified organisms

Activity (2010-2012)
Service users: 60
Trained users: >500

Economic impact (2010-2012)
Internal users: 30.0 k€
TOTAL: 30.0 k€

Scientific Services: General Weaknesses, Threats and Solutions

General Weaknesses & Threats

A recent survey of the scientific services at the CNB led to the identification of three major weaknesses:

Insufficient budget for the renewal of equipment that has become obsolete or defective

The continuous maintenance, upgrade and renewal of scientific-technical equipment is crucial for services that cope with a highly dynamic and rapidly changing technological context (e.g. Electron Microscopy, Confocal Microscopy, X-Ray Crystallography, Proteomics) or rely on the use of IT equipment with an extremely short life-cycle (e.g. Bioinformatics Initiative). Lack of economic resources for the renewal of obsolete equipment and, in many cases, even for the maintenance or substitution of basic equipment that has become defective or just simply worn out (e.g. installations in the Animal Facility, cytometers, centrifuges and rotors) have been identified by 9 CNB services as a major weakness that puts at risk the competitiveness of their respective services. This issue is particularly relevant in the case of services that are strategic for the CNB because of their essential role for the Centre's core research activities and their international visibility in the context of large-scale research platforms such as, among others, Electron Microscopy, Confocal Microscopy, X-Ray Crystallography, Proteomics, Flow Cytometry and Bioinformatics services. Furthermore, beyond the urgent need of maintaining existing facilities, investments in the implementation of novel state-of-the art technologies (e.g. modern High-Resolution Electron and Optical Microscopy equipment) will be essential to successfully defend the position of the CNB at the forefront of science.

Insufficient scientific-technical personnel

Although decreased funding of research projects is accompanied by a diminished demand for scientific services, and despite recent efforts of the CSIC to stabilise technical personnel, 10 services declare that they are understaffed and that lack of highly qualified and stably contracted personnel negatively impacts on the quality and response time of their services. This problem is particularly overt in

the case of Electron Microscopy, Flow Cytometry, Transgenesis, Bioinformatics Initiative, Proteomics and *In Vitro* Plant Culture.

Organisational deficiencies

Further weaknesses identified by CNB services that form part of the technological platforms on the UAM+CSIC International Excellence Campus, in particular Genomics, Transgenesis, Histology and Mouse Embryo Cryopreservation, point to administrative hurdles (lack of homogenous cost calculation and billing system) and operational inefficiencies (non-competitive response time and costs).

Conclusion: The current economic constraints have a dramatic negative impact on the quality and competitiveness of scientific services at the CNB, with many of them approaching a complete collapse.

Possible Solutions

In order to reduce costs and gain in efficiency, the CNB will continue implementing a strategy of **integration and smart specialisation**, prioritising the development of potent and internationally competitive in-house services that are strategic for the Centre's research and international visibility (advanced imaging technologies, Proteomics, Functional Mouse Genetics, Bioinformatics & Computational Biology), promoting the outsourcing and sharing of non-strategic or excessively costly services (e.g. high-throughput sequencing), and completing the integration of other services, in particular in the areas of Metabolomics, Optical Microscopy, Electron Microscopy and Nuclear Magnetic Resonance, into local (CEI-UAM+CSIC), regional (N+MADBIO), national (e.g. REMOA, National Centre for Electron Microscopy) and international (e.g. ESFRI) large-scale technological platforms. Of note, the seamless and efficient integration of CNB services into technological platforms of the CEI UAM+CSIC will require an institutional agreement on the **administrative and economic models that guarantee the long-term viability, efficiency and competitiveness of the CEI UAM+CSIC technological platforms**.

As emphasised above, there is an urgent need to **finance the maintenance and renewal of equipment** in order to guarantee that a large community of users will keep benefiting from the (still) excellent scientific services provided by the CNB. Attempts to cope with the economic problems that threaten the quality and, in some cases, viability of scientific services at the CNB include increasing

efforts to attract external clients and increase the number of installations that are made available to for-profit users (e.g. P3 biosafety laboratories). A better integration of the services into the scientific activities of the Centre is also expected to enable them to apply for research grants (e.g. the Head of the Transgenesis service is PI of a project funded by the National Research Plan). The renewal of large equipment (e.g. electron microscope), however, in general cannot be financed through standard research projects and will largely depend on the availability and/or restoration of CSIC/governmental funding programmes that are specifically launched to fund the maintenance, renewal, upgrade and *de novo* acquisition of scientific-technical equipment.

Recent efforts of the CSIC have enabled the CNB to stabilise personnel ascribed to its scientific services. This successful strategy of progressive **stabilisation of highly qualified personnel** should be continued to eliminate the still existing inefficiencies caused by an excessive rotation of personnel, which does not allow to fully capitalise on their time consuming and costly training.

Critical Analysis (SWOT)

Strengths

The **scientific excellence** of the CNB is at the basis of its outstanding international reputation and scientific leadership. Between 2008 and 2012, CNB scientists authored 1,153 publications - among them 959 SJR-indexed articles with an assigned impact factor - that summed 5,686 impact points with a mean impact factor of 5.9. According to the *Scopus* database, CNB publications were cited 49,024 times between 2008 and 2012 with an Hirsch (h)-Index of 131 (i.e., of the documents considered for the h-Index by *Scopus*, 131 have been cited at least 131 times). Articles published between 2008 and 2012 by the CNB received to date (September 2013) a total of 17,947 citations with an h-index of 58, which is in the range of leading Spanish research centres in the Life Sciences field, such as for example the CRG (*Centro de Regulación Genómica*, h=58). According to the recently published *SciMago* Institutions Ranking 2013 that analyses the scientific output of 3,315 institutions all over the world in the period 2007-2011, the CNB occupies the 49th position in the world and the 3rd position in Spain - only behind the ICIQ (*Instituto Catalán de Investigación Química*) and the CRG - in terms of quality of its publications, quantified as the percentage of publications in the first quartile (Q1) of top-ranked scientific journals in their respective area of knowledge; the CNB published 85.3% of its scientific articles in Q1. The *SciMago* report corroborates the scientific excellence of the CNB with other bibliometric parameters, such as normalised impact (1.7), excellence rate (25%), international collaboration (51%) and scientific leadership (47%). These values position the CNB within the upper range of Severo Ochoa Centres of Excellence in the Life Sciences field (CRG, CNIO, CNIC, IRB, EBD).

The outstanding scientific performance of the CNB builds on **leading-edge research facilities and services** that have positioned the Centre on the roadmap of international projects aimed at shaping science globally, such as the INSTRUCT Image Processing Centre, the ESFRI reference centre for image processing in Electron and X-Ray Microscopy within the largest European infrastructure for Structural Biology; the European Mouse Mutant Archive and ESFRI Project INFRAFRONTIER, European hubs for large-scale phenotyping and archiving of mouse mutant lines; and the participation of the CNB in the Human Proteome Project, coordinating work on the proteome of chromosome 16. The Protein Tools Unit at the CNB forms part of the EuroMAbNet, the European network of laboratories specialised in the production and use of monoclonal antibodies with the aim to share the most up-to-date technology and create common strategies to increase and standardise monoclonal antibody production.

Furthermore, the Scientific Computing Service actively engages in international initiatives, such as EMBnet and SOIBIO (the Iberoamerican Society for Bioinformatics). In addition to these international technology platforms, the CNB hosts 20 scientific services that signed between 2008 and 2012 a total of 707 contracts with external clients. Scientific services at the CNB have made important contributions to the integration of dispersed local resources in large-scale research platforms in the context of the International Campus of Excellence of the *Autónoma* University and the CSIC (CEI UAM+CSIC).

A major asset of the CNB is its **multidisciplinarity**. The Centre's research covers key areas of contemporary red and green Biotechnology, including Structural Biology, Molecular and Cellular Biology, Virology, Microbiology, Plant Genetics, Oncology and Immunology, in all cases with special emphasis on transferring the basic knowledge generated into biotechnological applications that benefit society. The Centre's broad research scope is also exemplified by the distribution of its publications into 30 different subject areas including, among others, Biochemistry, Genetics & Molecular Biology (35%), Medicine (16%), Immunology & Microbiology (15%), Agricultural & Biological Sciences (12%), Computer Science, Neuroscience, Environmental Science, Materials Science, Engineering etc.

The international visibility of the CNB and its capacity to attract talent are at the basis of its **internationalisation**. A considerable portion of the centre's scientific output in the past five years - 51% of its publications - are the result of international collaborations with 910 researchers in 59 different countries, including the USA (21%), United Kingdom (15%) and Germany (12%). The participation of CNB scientists in 46 FP7 project between 2008 and 2012 generated a network of collaborations with 310 research groups in 35 countries, including partners from third countries, such as the USA, Canada, Chile, South Africa, India, Vietnam, Honk Kong and China. The capacity of the CNB to attract foreign scientists has increased considerably in the past years. While in 2008 the CNB hosted 66 foreign scientists (11% of total staff), in 2012 the number of foreigners reached a new maximum with 138 people, which corresponds to 27% of total staff.

Another major asset of the CNB is its strong focus on **innovation**. The creation of a Technology Transfer Office in 2010 was instrumental to foster the centre's activity in generating and protecting intellectual property and establishing collaborations with industrial partners. Between 2008 and 2012, the CNB filed 38 patent applications to protect new inventions, 32 patent applications for entry into the international phase (PCT), and 21 applications for entry into the national phase (NBT). In this period, 17 license agreements as well as 169 research contracts and agreements have been signed with industrial partners.

The operation of an Outreach Office (since 2009) is at the basis of the Centre's strength in **scientific divulgation and communication**. The Outreach Office creates scientific awareness about modern Biotechnology and educates the public and various stakeholders about their perceived or potential risks and benefits through a website with specific contents directed to both scientists and the general public, including cartoons, videos and other classroom resources for primary and secondary education, as well as through social communication in Facebook and Twitter (approximately 3,600 followers in September 2013) and networking with science journalists. Furthermore, CNB scientists are encouraged to take active part in national science and education fairs, training activities for high school students and their teachers, open-house days for schools and the general public. CNB scientists also author blogs in leading national newspapers, participate in radio and TV broadcasts, and have published several books for the general public and high school students.

The sum of the Centre's strengths outlined above, have been crucial to consolidate the **outstanding fund raising capacity** of the CNB. Between 2008 and 2012, competitive funding of research at the CNB included 271 newly initiated projects, obtaining 36 M€ and 21 M€ from national and international funding bodies, respectively. In addition, 876 contracts for research and scientific-technical services generated a total income of 16 M€. When comparing external funding of CNB (projects, research contracts and services) with governmental funding through the CSIC, including salaries, operating costs and investments in infrastructure (caps. I, II and VI), the CNB achieves a ratio of 1.3. This means that the CNB raises 1.3-times more external funding than the economic contribution made by the CSIC. This ratio of external *versus* governmental funding is considerably higher than that of excellent research centres of comparable size, such as the CNIO that achieves a ratio of only 0.9 in the 2008-2012 period.

Weaknesses

The **loss of national funding** severely affects the capacity of the CNB to finance its research endeavours. When comparing competitive funding in the 2007-2009 period with the 2010-2012 period - triennial periods were chosen to eliminate interannual fluctuations - the CNB lost 10.2 M€ in terms of income through national R&D funding sources, which is equivalent to a decrease of 24%. This decrease was caused both by a dramatic reduction of national competitive funding (-7.8 M€; -26%) and a considerably diminished income through research contracts and services with mostly national clients (-2.4 M€; -20%). The 7.8 M€ decrease of competitive national funding implicated reduced funding by all

national funding bodies, including the Science Ministry (-2.8 M€; -13%), the Health Research Institute Carlos III (-2.2 M€; -58%), the Regional Government of Madrid (-2.4 M€; -65%) and Foundations (-0.4 M€; -38%). The decreased amount of national funding is apparently not due to a loss of the Centre's competitiveness, as indicated by its success in raising competitive funding from international, mainly the European Commission, funding bodies; international funding in the 2010-2012 period increased by 22% (+2.1 M€) as compared to the triennium 2007-2009. Nonetheless, the Centre's increased capacity to raise international competitive funding only compensated a small part (21%) of the dramatic loss at the level of national funding, research contracts and scientific-technical services, which reflects on the insufficient success of the CNB in accessing alternative funding sources.

Insufficient human resources are another major weakness of the Centre. The reduction of the overall budget of the CNB by 29% in 2012 (20.4 M€) as compared to 2010 (28.8 M€) was accompanied by a 15% reduction of CNB staff. This decrease puts at risk the continuity of various lines of research, in particular of smaller research groups headed by young group leaders (e.g. *Ramón y Cajal* fellows who have been recruited to start their career as independent researchers). Budgetary constraints impede the dynamic renewal of the Centre's research groups with young scientists. For example, the Centre's successful "Emerging Scientists" programme, designed to attract young and highly talented scientists, most of them through *Ramón y Cajal* contracts, cannot be continued due to lack of funding. Beyond budgetary constraints, another bottleneck for hiring young researchers, in particular when they are foreigners, are the human resources policies imposed by the Government/CSIC. The Centre's lack of autonomy and flexibility regarding the management of its human resources, general hiring restrictions and bureaucratic hurdles regarding the signing of contracts with foreign scientists are a major obstacle for international collaboration and incoming mobility (e.g., the homologation of academic titles is a requisite for signing a contract; the participation in the international *la Caixa* PhD programme requires documented knowledge of the Spanish language and being registered at a Spanish University at the time of application).

The already slightly but constantly **decreasing scientific output** of the CNB during the past triennium - and data available so far for 2013 corroborate this negative trend - is closely correlated with reduced funding and loss of personnel. The number of impact factor points produced per year by a scientific institution reflects both on its total scientific production (number of publications) and the quality of the published articles (impact factors of the journals in which the articles were published). Since 2010, the total number of impact points has already decreased by 8%. Taking into account the close correlation between available resources (budget & personnel) and scientific output (impact factor

points), as well as the obviously delayed impact of reduced funding on the number and quality of publications (see above), one may expect a substantial decrease of the centre's scientific output - in the order of −30% - during the next 2-3 years.

Threats

Since 2010, a reduction of funding through both the CSIC and external sources has diminished the total budget of the CNB in only three years by almost 30% from 28.9 M€ to 20.4 M€. This **budget is insufficient to maintain and renew basic scientific equipment and infrastructure**; and it is also **insufficient to adapt the Centre's research facilities to the current state-of-the-art**. This is particularly critical in the case of international infrastructures in advanced Electron Microscopy, Proteomics and Functional Mouse Genetics that provide the CNB with international visibility and (still) sustain its excellent reputation in Europe as a competitive hub of leading-edge technology and science.

As mentioned above, **budgetary and regulatory constraints obstruct hiring of scientists**, in particular of foreign researchers, which seriously **puts at risk the Centre's capacity to renew its scientific staff**. Of note, and this applies to virtually all research centres of the CSIC, an elevated number of scientific leaders at the CNB are approaching the end of their professional career, which implies an urgent need for the timely incorporation of new groups in order to guarantee the continuity of the Centre's scientific leadership. Incorporation of young and highly talented scientists is also essential to replace research lines that tend to become out-dated by novel and contemporary research approaches at the forefront of science. Furthermore, the continuous reduction of the Centre's scientific personnel is approaching a red line, below which the CNB will not have the critical mass of researchers that is needed to sustain internationally competitive and multidisciplinary research at the forefront of science.

Conclusion: The combination of two adverse circumstances, both of them due to insufficient funding, namely i) obsolete, defective and sub-optimal research infrastructures, and ii) the lack of timely renewal of scientific staff with highly talented and young people, will have an inexorable and dramatic negative impact on the scientific output of the Centre, both in terms of quantity and quality. The anticipated loss of scientific leadership and competitiveness will seriously impair the capacity of the CNB to compete for external funding and, consequently, further exacerbate the Centre's budgetary problems.

Opportunities

The initiation of novel and interdisciplinary lines of research, in particular in the areas of Structural Biology, Synthetic Biotechnology, and Bioinformatics & Computational Biology, that capitalise on the Centre's multidisciplinary research of excellence provide an opportunity to **renew the Centre's research programme and align it with the goals of the 'Horizon 2020' Programme**.

A stronger focus of the Centre's research programme on real-life challenges, together with an improved management of its portfolio of inventions and service offer, is anticipated to open novel opportunities for **technology transfer and funding through research contracts with industry and scientific services**.

A reinforced support for translational research, scientific management, training, and social communication, together with an increase of critical mass through the integration of the Centre's resources in large-scale research platforms and projects, is anticipated to open the **access to alternative funding sources**.

In addition, an **increased autonomy and flexibility**, in particular regarding the Centre's human resources policies will be of pivotal importance to maintain the competiveness of the CNB. Of note, there is broad consensus that the success of direct competitors of the CNB, such as the *Severo Ochoa* Excellence Centres CRG, IRB, CNIC and CNIO, relies on their management system; all of them are public foundations, combining the stability provided by public financing with the autonomy and flexibility associated with the private sector, which has enabled them to attract talent and dynamically adapt their scientific staff to a rapidly changing and extremely competitive context of globalised scientific research.

Selective Advantages

- Broad and multidisciplinary research programme based on scientific excellence.
- Scientific services with broad coverage of key technologies in contemporary Life Science research.
- Integration of research facilities in national and international large-scale technological platforms.
- High potential to transfer knowledge and technology to the public and private sectors.

Objectives & Strategies

General Strategy

Objectives

In the scenario of a continuously decreasing budget and loss of scientific personnel (see SWOT analysis), the CNB devises a realistic and defensive strategy for the next four years that will focus on three major objectives:

i) Preserve the scientific quality and leadership of the CNB.
ii) Retain a critical mass of young and highly talented scientists.
iii) Improve the critical financial situation of the Centre.

Proposed Actions

PRESERVE THE SCIENTIFIC QUALITY AND LEADERSHIP OF THE CNB

Scientific excellence is at the basis of the Centre's capacity to raise funding for its research endeavours and to efficiently transfer the outcomes of its research to the public and private sectors for the benefit of society. Thus, a major focus of the present Action Plan will be on the Centre's research programme and technology transfer capacities.

The CNB will implement five strategic actions:

i) Create critical mass and synergies in a scenario of a dramatic reduction of scientific personnel and funding by integrating the Centre's research lines into a scientific programme with a common focus on four big global challenges, namely Infectious Diseases, Inflammation & Cancer, Sustainability of Food Production, and Environmental Pollution.
ii) Defend the Centre's position at the forefront of modern Biotechnology by launching new and ground-breaking research endeavours in the incipient area of Synthetic Biotechnology.
iii) Preserve the Centre's capacities to engage in bold and long-term exploratory projects by consolidating its internationally recognized research platforms in strategic areas of Structural and Functional Biology.
iv) Sustain the progressive implementation of quantitative Biology approaches at an internationally competitive level through the creation of a Bioinformatics & Computational Biology Platform.

RETAIN A CRITICAL MASS OF YOUNG AND HIGHLY TALENTED SCIENTISTS

Renewal of the Centre's research lines and the planned implementation of novel research endeavours will critically depend on the Centre's capacity to train and attract young, talented and highly motivated scientists. The CNB, however, has to cope with a progressive loss of PhD students and postdoctoral scientists, scarcity of new tenure track positions, reduced funding, general hiring restrictions, bureaucratic hurdles regarding the hiring of foreign personnel, and a generalised lack of autonomy to hire personnel. To counteract the persistent erosion of the centre's human resources, the following four actions will be implemented:

i) Exploit the whole spectrum of funding instruments and mechanisms for the recruitment of young group leaders.
ii) Align the centre's postdoctoral training programme with the objectives of its research programme in terms of favouring interdisciplinary training with a focus on societal challenges and innovation.
iii) Increase the visibility of the CNB for highly talented and motivated PhD students through outreach and extracurricular training activities.
iv) Promote training of CNB scientists in innovation and entrepreneurship, as well as facilitate their complementary training in industry.
v) Promote international mobility through institutional agreements and facilitate the incorporation of foreign staff through dedicated support personnel.

IMPROVE THE CRITICAL FINANCIAL SITUATION OF THE CENTRE

Extraordinary efforts are already being made by the CNB to cope with the budgetary constraints that put at risk the scientific excellence and leadership of the Centre. A key element of the centre's strategy to leverage the scientist's desperate efforts to raise funding and to access to alternative funding sources, will be to improve support for the management of research, innovation and communication by implementing the following three actions:

i) Reinforce dedicated support for Scientific Management in order to expand funding opportunities and improve success rates in competitive fund raising.
ii) Intensify and professionalise support for Technology Transfer in order to increase income through license agreements and the exploitation of scientific services, research infrastructures and technical consultancy.
iii) Leverage the Centre's efforts to obtain external funding by increasing the visibility of the CNB through social communication, scientific events, dissemination of its research results and scientific divulgation.

Scientific Strategy

Objectives

FOCUS ON GRAND SOCIETAL CHALLENGES

The CNB will achieve critical mass and create synergies by promoting the convergence of its research lines on four well-defined areas that represent grand societal challenges on the research agenda of the forthcoming European framework programme 'Horizon 2020', such as Infectious Diseases, Inflammation & Cancer, Sustainability of Food Production, and Environmental Pollution.

IMPLEMENT SYNTHETIC BIOTECHNOLOGY APPROACHES

The CNB aims to realize the huge potential of Synthetic Biotechnology to tackle the four big global challenges mentioned above. This strategy is supported, among others, by the Centre's: i) broad, comprehensive and multidisciplinary research approach; ii) wide range of technological capacities, including the genetic and metabolic engineering of pro- and eukaryotic systems, as well as the analysis of their structural and functional properties at the single molecule level; iii) long-standing expertise in large-scale 'omics' endeavours, such as for example the Human Proteome Project, mapping of the pathogen 'resistome' or exploring the plant cell 'transportome'; iv) accumulating expertise in the design and assembly of complex biological systems with new-to-nature functions for biotechnological applications, such as for example the engineering of bacteria and plants for bio- and phytoremediation purposes; v) European leadership in the development of material and computational standards that enable the forward-design and assembly of prokaryotic systems far beyond the limitations of traditional genetic engineering (ST-FLOW, FP7 project coordinated by the CNB); vi) international recognition of the excellence of flagship projects at the forefront of Synthetic Biology (2 Advanced ERC grants, FP7 and HFSP funding).

STRENGTHEN RESEARCH PLATFORMS

Another objective of the Centre's scientific programme will be to increase its visibility on the roadmap of pan-European research platforms by consolidating its participation in international infrastructures in the strategic areas of Imaging, Proteomics and Functional Mouse Genetics. An additional and novel strategic priority will be to substantially expand already existing - but still suboptimal - computational resources, bioinformatics support and expertise in computer simulation and modelling of complex biological systems through the creation of a

powerful and internationally competitive Bioinformatics & Computational Biology Platform.

Proposed Actions

FOCUS ON GRAND SOCIETAL CHALLENGES

Challenge 1: Infectious diseases
The Cellular & Molecular Biology Department's outstanding expertise in Virology, together with ground-breaking contributions of the Macromolecular Structures Department regarding structure-function relationships that govern viral infections, as well as the Microbial Biotechnology Department's advances in understanding and combating microbial infections, have enabled the CNB to generate a unique portfolio of innovative vaccination strategies against infections with a major impact on Public Health (AIDS, SARS, hepatitis C, influenza, leishmaniasis, malaria) as well as novel therapeutic approaches to combat *Mycobacterium* and *Streptococcus* infections. A priority for the next years will be to push the most promising vaccine candidates forward in the R&D pipeline by initiating GMP production, pre-clinical and early clinical studies. A mid-term goal will be to nucleate these activities around a Vaccine Development Platform (see Proposed Actions in the Technology Transfer section). Furthermore, the Microbial Biotechnology Department's highly interconnected research lines will focus on regulatory circuits, genes and protein networks involved in the response of bacteria to stressful environments, in particular their response to antibiotics, in order to develop innovative strategies to cope with the threat of antibiotics resistance.

Challenge 2: Inflammation & cancer
Research in the Department & Immunology and Oncology addresses important aspects of inflammation and cancer, with special emphasis on characterising the cellular and molecular mechanisms that underlie tumour immunology, infections and autoimmunity. Based on a detailed analysis of the intracellular signals triggered by specific receptors in activated immune cells that are responsible for cell expansion, differentiation, migration, and/or induction of a specific differentiation process, as well as the molecular changes that trigger cell transformation, the goal is to characterize the basis of the immune response, to propose improved approaches that would limit the immune response in chronic inflammation, and to identify novel targets for the prevention, diagnosis and treatment of cancer. Scientific advances made by this Department in the fields of signalling, cell motility, epigenetic or chromatin stability, are contributing to the development of improved approaches for immune response modulation during infection and inflammatory reactions, as well as to the identification of novel

targets for cancer diagnostics and therapy. Furthermore, the Centre's research within the Human Proteome Project focuses on chromosome 16, encoding numerous proteins that are relevant to the regulation of immune cell function and inflammation-driven carcinogenesis. Work in the Cellular & Molecular Biology Department on transcriptional responses in immune cells and molecular mechanisms underlying inflammation and metastasis, as well as studies in the Macromolecular Structures Department on receptor-ligand recognition with cell surface proteins engaged in the regulation of the immune system also integrate in the Centre's broad and multidisciplinary approach to tackle the challenge of inflammatory and neoplastic diseases.

Challenge 3: Sustainability of food production

Research in the Plant Molecular Genetics Department converges on the goal to elucidate mechanisms that govern adaptive responses of plants to different forms of environmental and pathogenic stress, as well as to advance our understanding of how this multi-stress response is linked to concomitant constraints in growth and crop production. Based on the proof-of-concept that the pathways regulating stress and development can be genetically uncoupled and function independently from each other, the ultimate goal is to obtain stress-resistant plants that maintain high biomass and crop production under adverse environmental conditions. This work is based on the identification of key transcription factors regulating stress responses and development processes, as well as on the evaluation of their biotechnological potential in crop species, such as brassica, tomato and potato. To further extend this line of research from genetic and genomic studies to proteomic and metabolic profiling of the plant multi-stress response regulatory networks, the recruitment of experts in these fields is planned. Close collaborations with the Centre's Functional Proteomics and Systems Biology platforms will be instrumental to strengthen and fully develop this line of research during the next years.

Challenge 4: Environmental pollution

Novel knowledge generated in the Plant Molecular Genetics Departments on the masterswitches that link adaptive stress signalling to the regulation of development, transport, storage and metabolic circuits in plant cells (see above) will also drive the implementation of novel strategies for the use of plants for phytoremediation purposes. Similarly, research projects developed by the Microbial Biotechnology and Systems Biology Departments aim at understanding the adaptive response of bacteria to environmental stress and to translate this knowledge into the design of circuits that allow programming of bacteria for their use as bacterial biosensors and bioremediation strategies. These projects will heavily rely on technological support by the Centre's Genomics, Proteomics and Metabolomics facilities, and also require the implementation of novel

computational approaches to model the efficiency and environmental impact of complex biological systems.

IMPLEMENT SYNTHETIC BIOTECHNOLOGY APPROACHES

The following section describes three incipient research lines that reflect on the Centre's goal to implement leading-edge Synthetic Biotechnology approaches. These projects focus on the engineering of protein modules, cell division machineries and antibody-producing circuits with new-to nature functions that are anticipated to open a whole realm of ground-breaking biotechnological tools for a wide range of applications.

Synthetic nanodevices

A senior group leader (Víctor Muñoz) has been attracted very recently to initiate a multidisciplinary research line at the CNB aimed at the identification of novel connections between protein folding and function. Funded by a recently awarded Advanced ERC grant, his research approach will combine single molecule and high-resolution NMR spectroscopy with protein engineering, molecular biophysics and high-performance computer modelling to explore the functional implications of continuous conformational changes of protein modules upon unfolding (downhill folding). The two major objectives of this work are i) to provide the proof-of-concept that such conformational rheostats can be used for building of high-performance, ultrafast, single-molecule sensors, and ii) to explore the roles of conformational rheostats in the regulation of three fundamental processes in molecular biology, namely coordination of protein networks, DNA sliding and homing-to-target of transcription factors, and molecular springs in macromolecular assemblies. The planned implementation of novel high-resolution NMR spectroscopy approaches, an essential step in the implementation of this research line, will also greatly benefit other research projects of the CNB at the forefront of Structural Biology.

Synthetic Biology of cell division

Under the leadership of a senior group leader (Miguel Vicente), and financed by the Human Frontiers Science Program (building on the results of a previous FP7 project coordinated between 2009 and 2013 by this scientist), this line of research deals with an apparent paradox, producing bacterial cell division without cells. Its objective is to reconstruct a functional divisome, the molecular engine required for bacterial division, in the test tube. The initial steps include reconstructing a proto-ring, the first structure in the assembly of the divisome, and reproducing the septum positioning mechanisms. The planned implementation of high-resolution optical microscopy technology will provide the spatial resolution required to clarify the missing details on the architecture of the

bacterial division machinery. The results will help usher in the new field of synthetic biology of cell division and lead to new pharmacological applications, including antimicrobials to attack Gram-negative pathogens.

Synthetic immune system

One of the centre's most ambitious Synthetic Biotechnology endeavours during the next years will be to assemble and optimize an artificial immune system, constructed exclusively with prokaryotic building blocks. This line of research pursues the all-in-one generation, optimisation and production of antibodies by a bottom-up engineered system with new-to-nature system properties devoid of the limitations that are inherent to the immune system of vertebrates. The initial phase of this long-term project is funded by a recently awarded Advanced ERC grant to Víctor de Lorenzo. It is planned to reinforce this line of research by recruiting a group leader who will develop novel computational approaches for the modelling of networks that govern the interplay between genotype, phenotype and biological efficacy in synthetic systems.

STRENGTHEN RESEARCH PLATFORMS

International research platforms

To capitalise on investments made in the past, a major goal for the next years will be the consolidation of three of the Centre's major international infrastructures that are of strategic importance both for in-house research and international collaborations in the areas of Imaging (INSTRUCT Image Processing Centre), Proteomics (Human Proteome Project) and Functional Mouse Genetics (ESFRI projects EMMA & INFRAFRONTIER). Related to the Centre's role as European hub for Electron and X-Ray Microscopy image processing, the CNB will keep pursuing the long-standing goal to create a regional or national Electron Microscopy Platform.

Creation of a Bioinformatics & Computational Biology Platform

The Centre's growing portfolio of 'omics' and Systems Biology projects, as well as its role as European Reference Centre for advanced image analysis in Electron and X-ray Microscopy, generate an exponentially increasing amount of data that need to be stored, analysed, modelled, integrated and interpreted to extract meaningful information and knowledge. In this context, an upgrade of the Centre's computational infrastructure and, most importantly, the recruitment of renowned experts in Bioinformatics and Computational Biology are a priority for the next years. Beyond the mission to just simply meet the increasing technical needs of the centre, these efforts will be guided by the vision to induce a qualitative leap in the Centre's research by providing the CNB with a potent and internationally competitive Bioinformatics & Computational Biology Platform. The

creation of this novel platform will capitalise and continue elaborating on recent efforts to improve the visibility and coordination of the existing Bioinformatics services at the CNB through the creation of a Bioinformatics Initiative that integrates six areas:

- Computational Genomics: This service is part of the Genomics Unit and provides bioinformatics support for the analysis, visualization and interpretation of genomics-related projects, including microarrays and next generation sequencing. Lead scientist: Juan Carlos Oliveros (http://bioinfogp.cnb.csic.es).
- Sequence Analysis and Structure Prediction: Provides Bioinformatics support for sequence analysis and protein structure prediction. Lead scientist: Mónica Chagoyen Quiles (http://pdg.cnb.csic.es/bioservice_en.html).
- Scientific Computing: Covers general scientific data analysis needs and maintenance of the national EMBnet node. Lead scientist: José Ramón Valverde (http://sci.cnb.csic.es/).
- Computational Proteomics: This service is part of the Proteomics Facility and provides interpretation, validation and reporting of data derived from Proteomics experiments. Lead scientist: Alberto Medina Auñon (http://proteo.cnb.csic.es).
- Functional Analysis: This service is part of the Functional Bioinformatics group and provides functional analysis of high-throughput experiments, such as microarrays and next generation sequencing studies. Lead scientist: Alberto Pascual Montano (http://bioinfo.cnb.csic.es).
- Statistical Analysis: This service provides statistical support and consultancy from experimental design to complex statistical data analysis. Lead scientist: Carlos Oscar Sánchez Sorzano (http://biocomp.cnb.csic.es/~coss).

Technology Transfer

Objectives

A priority for the CNB during the next years will be to boost the Centre's capacity to transfer its research results to the public and private sectors by professionalising the management of patents and licences, as well as the identification and networking with key players in the Health and Agriculture sectors, and the implementation of joint ventures with industrial partners. Dedicated support will be implemented to enable the Centre’s researchers to initiate joint ventures with industrial partners, hospitals and contract research organisations. Furthermore, in order to empower scientists at the CNB to

translate their research results into viable business ideas and, eventually, the creation of spin-off companies, business training and mobility strategies will be implemented (see Training section).

Proposed Actions

Technology transfer
Additional personnel will have to be recruited in order to further intensify and professionalise technology transfer at the CNB. Efforts will be made to pro-actively offer scientific-technical infrastructures and services at the CNB to academic, public and industrial users in order to pave the way for novel collaborations and joint ventures. Another important goal will be to channel the highly demanded, but rather dispersed, capacities of CNB researchers as scientific-technical consultants by implementing a professional consultancy service for external clients in the private and public sectors. Within the Centre's technology transfer strategy, a major objective will be to initiate GMP production, preclinical research and early stage clinical trials with its most promising HIV and SARS vaccine candidates. A mid-term goal will be to create a Vaccine Development Platform, providing a permanent support structure for the development of novel vaccines against prevalent human diseases. A major aim of this platform will be to articulate the participation of the CNB in the follow-up of the corresponding phase I/II clinical trials by performing immunological analysis of clinical samples.

Intersectoral mobility
The CNB plans to implement collaboration agreements with research-intensive enterprises that pursue several objectives regarding mobility of the Centre's students and staff, such as to i) provide PhD students the opportunity to realise part of their thesis project in an enterprise, ii) realise joint research projects and organise scientific events in the framework of public-private partnerships, and iii) offer *ad-hoc* training opportunities for CNB scientists and technicians in enterprises and, *vice versa*, offer enterprises training for their personnel at the installations of the CNB. Taken together, these actions are expected to improve multidisciplinary training, foster mobility between the public and private sectors, and facilitate the translation of research results from academia to industry.

Innovation training
Another key element to accomplish the centre's objective to combine scientific excellence with business innovation is described in the Training section (see below).

Training

Objectives

During the past four years, the CNB has been facing a progressive reduction of the number of staff scientists, new PhD students and postdoctoral researchers, which is anticipated to produce very soon a negative impact on the Centre's scientific productivity and on the dynamic renewal of its scientific personnel and research lines. Future strategies to attract young group leaders, PhD students and postdoctoral fellows through improved training programmes and dedicated support for foreign students (see internationalisation) aim at reverting this negative trend.

Proposed Actions

Incorporation of independent group leaders
Though virtually impossible in the current economic situation, but nonetheless of pivotal importance for the Centre's competitiveness in the future, efforts will be made to obtain funding and establish the mechanisms required to re-open the centre's 'Emerging Scientist Programme' for the recruitment of talented junior researchers – in particular Ramón y Cajal fellows – and provide adequate conditions for their career as independent researchers.

Postdoctoral training
To reinforce joint scientific endeavours across different research groups and departments, postdoctoral training at the CNB will be enriched through the implementation of 'Synergy Projects'. Synergy Projects will involve at least two research groups, preferably from different departments. Applications will be reviewed and prioritised by external evaluators. Selection of projects will be based on criteria of scientific excellence, relevance of the proposed project in the context of the grand societal challenges tackled by the Centre's research programme, and the potential synergies that can be expected from the proposed interdisciplinary approach. In the case of obtaining external funding (e.g. Ramón y Cajal contracts, COFUND Action, ITN, Severo Ochoa Excellence Award), the participation of CNB researchers in this initiative will be encouraged by allocating funds for personnel and small equipment.

Attraction of PhD students
A major route to attract PhD students to the CNB is the close collaboration of the centre with Spanish Universities, in particular with the *Autónoma* University of Madrid (UAM) in the context of the International Campus of Excellence (CEI) UAM+CSIC, which includes the exhaustive participation of CNB scientists in international PhD programmes and Master courses in Life Sciences and Medicine.

To increase the visibility of the CNB for university students, the CNB will further elaborate on the organisation of its international summer course on 'Introduction to Research' for students in the third and fourth years of any university degree in science. The course targets qualified and highly motivated students, selected in a competitive process, who would like to enter into contact with biotechnology research and eventually start their thesis at the CNB.

Innovation training
Efforts will be made to raise funding (e.g. ITN, COFUND, Severo Ochoa Excellence Award) for the implementation of business training grants that will enable selected CNB scientists to engage in part time business training at the IE Business School in Madrid, one of the world's leading business schools. The IE's international 'Management Fundamentals for Scientists and Researchers' programme, launched with great success in 2012, pursues the objective to provide scientists with complementary skills that enable them to render their research projects implementable and transferrable. Business training of CNB scientists will benefit the Centre in many ways; scientists with managerial skills will have the necessary skills to efficiently manage their scientific, economic and human resources also in the context of an academic research centre, they will know how to protect their research results and render them attractive for further development by industrial partners, they will have the knowledge and vision required to spearhead academia-business partnerships, and they will have the entrepreneurial spirit needed to launch new ventures, such as the creation of a start-up company.

Scientific Divulgation

Objectives

The CNB operates an Outreach Office with the mission to create scientific awareness about science and educate the public and various stakeholders about perceived or potential risks and benefits of modern biotechnology. The Office maintains a website with specific contents directed to both scientists and the general public, including cartoons, videos and other classroom resources for primary and secondary education. The Office also disseminates research results, issues press releases and elaborates printed and audio-visual material for science journalists. The organisation of meetings, workshops, lectures and practical courses for scientists, professionals in the Biotech sector and students facilitates contact with researchers worldwide. Future efforts will be directed to intensify these activities and further improve the interaction with the general public through the centre's website, Facebook and Twitter accounts.

Proposed Actions

Communication
The CNB will increase its presence in digital and social media by improving its website and increasing its activities in Facebook (www.facebook.com/CNB.csic) and Twitter (twitter.com/CNB_CSIC). Particular emphasis will be on educating the public about advances, perceived risks and benefits of incipient research areas in modern Biotechnology, such as Synthetic Biotechnology.

Outreach
The CNB will also increase its participation in national science and education fairs, its offer of training activities for high school students and their teachers, as well as open-house days for schools and the general public. Outreach activities will also include a new initiative aimed at targeting elementary school students. This activity will consist of visits of CNB scientists to elementary schools in order to explain research done at the CNB, as well as to communicate general concepts, challenges and advances of modern Biotechnology, using specifically elaborated audio-visual material and demonstrating easy-to-perform hands-on experiments.

Internationalisation

Objectives

As outlined in the SWOT analysis, the CNB has already reached an extraordinary level of internationalisation in terms of co-authorships with foreign scientists and the Centre's participation in international research projects and research infrastructures. Nonetheless, there is still much room for improving international mobility and rendering the Centre more attractive and friendly for foreign staff.

Proposed Actions

Scientific Management support
The planned reinforcement of dedicated support for Scientific Management will pursue the goal to expand scientific relationships with leading research institutions abroad and other international key stakeholders in order to enable the CNB to engage, effectively contribute and lead internationally relevant scientific initiatives.

International mobility

The CNB plans to establish agreements with international institutions to foster exchange of scientific and technical personnel. These agreements will capitalise on already existing scientific collaborations of the CNB with world leading research institutions. In line with the Centre's strategy to foster innovation training, institutional agreements that will facilitate the exchange of scientific and technical personnel for training and research purposes will also target enterprises (see above).

Dedicated support for foreign staff

Bureaucratic and logistic obstacles frequently cumber the initiation of a scientific career in a foreign country. In particular, the requisites to formalise a working contract, such as to obtain a residency permit, open a national bank account or homologate academic titles obtained abroad may be an extraordinarily frustrating experience for students and scientists who lack knowledge of the Spanish language, culture and administrative procedures. To overcome these obstacles, the CNB plans to reinforce the Human Resources Department with a dedicated support officer who will be in charge of providing foreign scientific and technical personnel with the advise and help they need to have a smooth and clear start of their professional career at the CNB. In this context, support in the CSIC headquarter, dedicated to resolving the barriers that render hiring of foreign scientists extremely difficult, if not impossible, would be extremely welcome.

NOTE: ***The implementation of the proposed Action Plan 2014-2017 and the viability of the CNB as an internationally competitive research centre will critically depend on the level of direct public funding (salaries, running costs, maintenance of infrastructure) and the availability of competitive funding sources (in particular research projects funded by the central and regional governments) during the next four years.***

Quantitative Indicators

As outlined in the SWOT analysis, since 2010, the total budget of the CNB has been diminishing at an average rate of almost 10% per year. At present, there is no convincing evidence that this situation will change substantially during the next years. Reduced funding of research projects, lack of investments in infrastructure and loss of scientific-technical personnel are progressively eroding the Centre's capacities to produce leading-edge science, raise competitive funding, train PhD students, attract postdoctoral researchers and engage in complementary activities, such as the organisation of scientific events and divulgation. The reduction of economic and human resources is anticipated to fully impact along the next years on the Centre's competitiveness. Under these circumstances, it appears reasonable to assume that the indicators that reflect on the Centre's scientific output and activities will decrease at the same pace as the budget (i.e., a yearly decrease in the range of 5% to 10%). Since scientific output is a delayed indicator of research funding, even in a more optimistic economic scenario for the second half of the 2014-2017 period, the Centre's output is expected to continue decreasing for some more years.

Año	Origen Dato	Nota Final	FINANCIACIÓN				TRANSFERENCIA				FORMACIÓN		VISIBILIDAD				
			Proyectos	Publicac	Congresos		Spin-Offs	Patentes Licenciadas	Contratos I+D	Patentes Solicitadas	Tesis	Cursos	Difusión		Internacionalización		
				Alto to	Medio	Bajo							Materiales	Eventos	Personal	Co-Autorías	Colaboraciones
2008	conCIENCIA		-	145 4	9	23			-	22	15		1	2	-	-	-
2009	conCIENCIA		-	171 10	17	22		1	-	14	34		2	4	-	-	-
2010	PCO	100	10.501.215,18	162		3,0			3.371.083,28	5	31				96	12	60
2010	conCIENCIA		-	181 13	10	27			-	19	37	98	1	3	-	-	-
2011	PCO	100	11.865.312,48	169 1,0	2,0	5,0		6	5.012.325,04	8	25	116	8	32	221	124	62
2011	conCIENCIA		-	197 12	19	34		8	-	19	35	306	12	33	-	-	-
2012	PCO	100	7.639.391,52	181 I1,0	7,0	6,0		4	3.189.904,67	2	25	51	30	22	240	156	64
2012	conCIENCIA		-	188 19	22	29		4	-	13	43	109	30	22	-	-	-
MEDIA	PCO	100,00	10.001.973,06	170,67 I,00	3,00	4,67		3,33	3.857.771,00	5,00	27,00	55,75	12,67	18,00	185,67	97,33	62,00
MEDIA	conCIENCIA			176,40 I,60	15,40	27,00		2,60		17,40	32,80	102,60	9,20	12,80			
2014	Centro		6.508.000	163 9	8	7	0	1	2.711.000	8	22	45	27	20	180	140	48
2014	VICYT																
2015	Centro		5.860.000	147 7	7	7	0	1	2.440.000	8	20	41	24	18	162	127	43
2015	VICYT																
2016	Centro		5.570.000	140 6	5	7	1	1	2.320.000	8	19	39	23	17	146	121	39
2016	VICYT																
2017	Centro		5.270.000	133 6	5	7	1	1	2.196.000	8	18	37	22	17	138	115	37
2017	VICYT																