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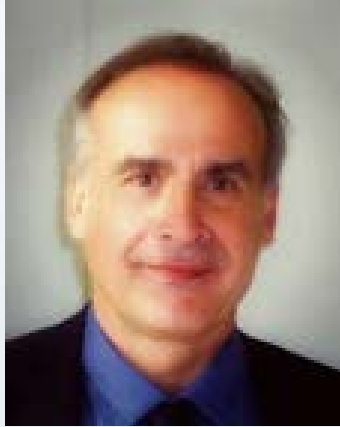
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P R E S E N T A T I O N



With almost thirty years of evolution, the Institute of Health Carlos III (ISCIII) has been configured as a baseline in the convergence of health research, scientific-technical services of reference, training and the National Health System.

Within the framework of the 2013-2016 State Plan for Scientific and Technical Research and Innovation, the Strategic Action in Health (AES) has as its principle to promote the health and well-being of citizens, as well as developing preventive, diagnostic, curative, rehabilitative and palliative aspects of disease. Novelties of the Strategic Action in Health in 2015 managed by the ISCIII include the incorporation of the Aid for Development Projects in Personalized Medicine; the summon for new research groups within the State Program for the Promotion of Scientific and Technical Research of Excellence allowed the incorporation of 11 new groups, and the i-PFIS summon IIS-Company in

Science and Technologies of Health Doctorate. The assistance of the State Mobility Subprogram, within the State Program for Talent Training and its Employability, allowed, as a novelty, the financing towards stays of the research staff hired under the AES. All of this coinciding with the design and implementation of the Management Improvement Plan of the Strategic Health Action aids.

During 2015, the Institute of Health Carlos III instructed the accreditation of seven new Institutes of Sanitary Research: IIS BIOCRUCES (Biocrucis Health Research Institute), IBIMA (Institute of Biomedical Research of Malaga), IMIB (Murcian Institute for Bio sanitary Research Virgen de la Arrixaca), IDIVAL (Marques de Valdecilla Research Institute), INIBIC (A Coruña Biomedical Research Institute), IIS Aragón (Aragon Health Research Institute) and IBS.GRANADA (Bio sanitary Research Institute of Granada). Moreover, IDIS (IIS Santiago de Compostela), IDIPAZ (IIS La Paz University Hospital) and IISFJD (IIS Foundation Jimenez Diaz) renewed their accreditation in 2015. The Accreditation Unit and the Technical Commission of Accreditations continued responding requests for information on requirements, conditions and accreditation processes of hospitals of the National Health System that contemplated the possibility of creating a Sanity Research Institute. Furthermore, the unit analyzed and reported on the validity of accreditation in the Institutes that have undergone major changes in their structure.

Some of the notable milestones that were reached by the Biomedical Research Network Centers (CIBER) faithfully reflect the commitment of the Institute of Health Carlos III towards improving the health and well-being of our fellow citizens, such as new diagnostic methods and the designation of a New Orphan medicinal product by the European Medicines Agency, patented by CIBERER researchers as well as the participation of its researchers in studies on the effectiveness of the vaccine against pertussis in pregnant women and the adequacy of the vaccination schedule. Worth noting is that at an international reference level, CIBERER participated in the new Joint Action on Rare Diseases (RD Action), the presentation in the European Parliament of the Mental Health research roadmap coordinated by CIBERSAM, and the participation of CIBERBBN as partner in the European Project DRIVE, in which biomaterials and new surgical devices for the treatment of diabetes will be developed. In addition, both from the Epidemiology and Public Health Area as well as from CIBER's Liver and Digestive Diseases Area, international studies have been conducted on the effectiveness of new treatments and participated in the Strategic Plan for the Approach of Hepatitis C in the National Health Plan.

Conversely, the scientific achievements of the National Center for Cardiovascular Research Carlos III (CNIC), the National Cancer Research Foundation (CNIO) and the Center for Research on Neurological Diseases (CIEN), described in the ISCIII 2015 Memoir, endorse these aforementioned centers as a national and international reference in their respective fields of research yet another year.

The Institute of Health Carlos III centers and units have participated in numerous scientific and technical activities throughout 2015. ISCIII centers actively participated in regards to the West African outbreak of the Ebola virus disease, ruling out all suspected cases of infection in travelers, health workers and donors who arrived to our country from the epidemic zone. They have also participated in the study of more than 200 outbreaks of contagious diseases, such as the cases of Chikungunya fever, West Nile fever and legionellosis associated with environmental exposures. Conversely, in December 2015 the first cases of infection by the Zika virus were detected, and were diagnosed in the National Center of Microbiology. The National Epidemiological Surveillance Network (RENAVE) that is coordinated by the National Epidemiology Center continued its work on notification, analysis and control of diseases in Spain, highlighting its role as a link between the surveillance systems of the Autonomous Communities and those of International organizations such as WHO (OMS) and ECDC. The development and implementation of the Surveillance System in Spain (SIVIES) has continued, which is an application that allows the electronic notification of cases of diseases with mandatory declaration or of epidemiological interest. The National Air Quality Reference Laboratory (LNRCAL) of the National Center for Environmental Health maintained its activity of supporting national systems for assessing ambient air quality, supporting the community's commitment for a cleaner atmosphere in Europe. Incidentally, in 2015 there was an increase in the number of users and inquiries to the Information Services of Rare Diseases, Congenital Anomalies, as well as the Rare Diseases Bio bank.

As for research activity of the ISCIII centers of reference, 2015 has been a productive year, with more than 250 projects and active research contracts, as well as management assignments and collaboration agreements. In addition, around 300 publications (more than 75% in journals in the first quartile of the specialty) and more than 500 papers and presentations at national and international congresses have been carried out. In this regard, it is important to recognize the work of our Research and Animal Welfare Ethics Committee, which has evaluated a total of 156 projects, both from the Institute of Health Carlos III and Foundations, as well as from external centers. Likewise, ISCIII Centers have also organized the III Congress of Bioethics on "Ethical Aspects of Access to Health Data".

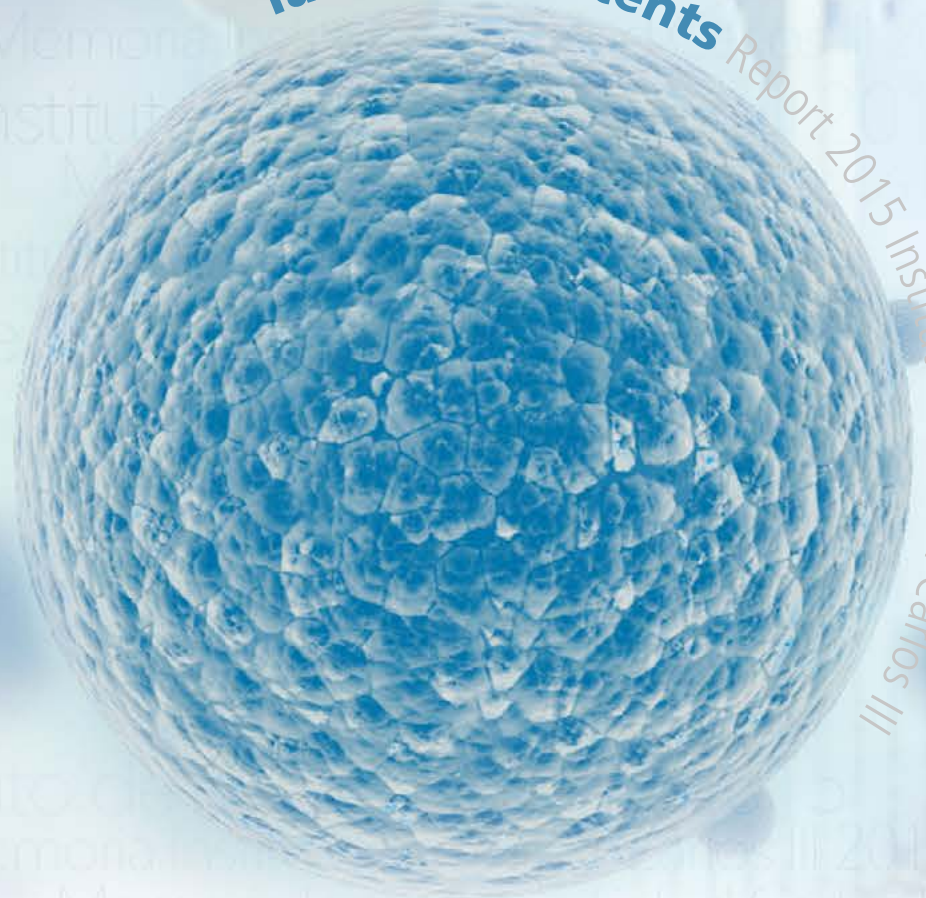
In terms of teaching activities, it is worth mentioning that the first academic year of the Microbiology for Public Health and Research in Infectious Diseases Master was completed in 2015, coordinated between ISCIII and the University of Alcalá de Henares. Altogether the National School of Health has imparted 3,236 class hours to a total of 352 students and the National School of Occupational Medicine has imparted 1,922 class hours to a total of 657 students.

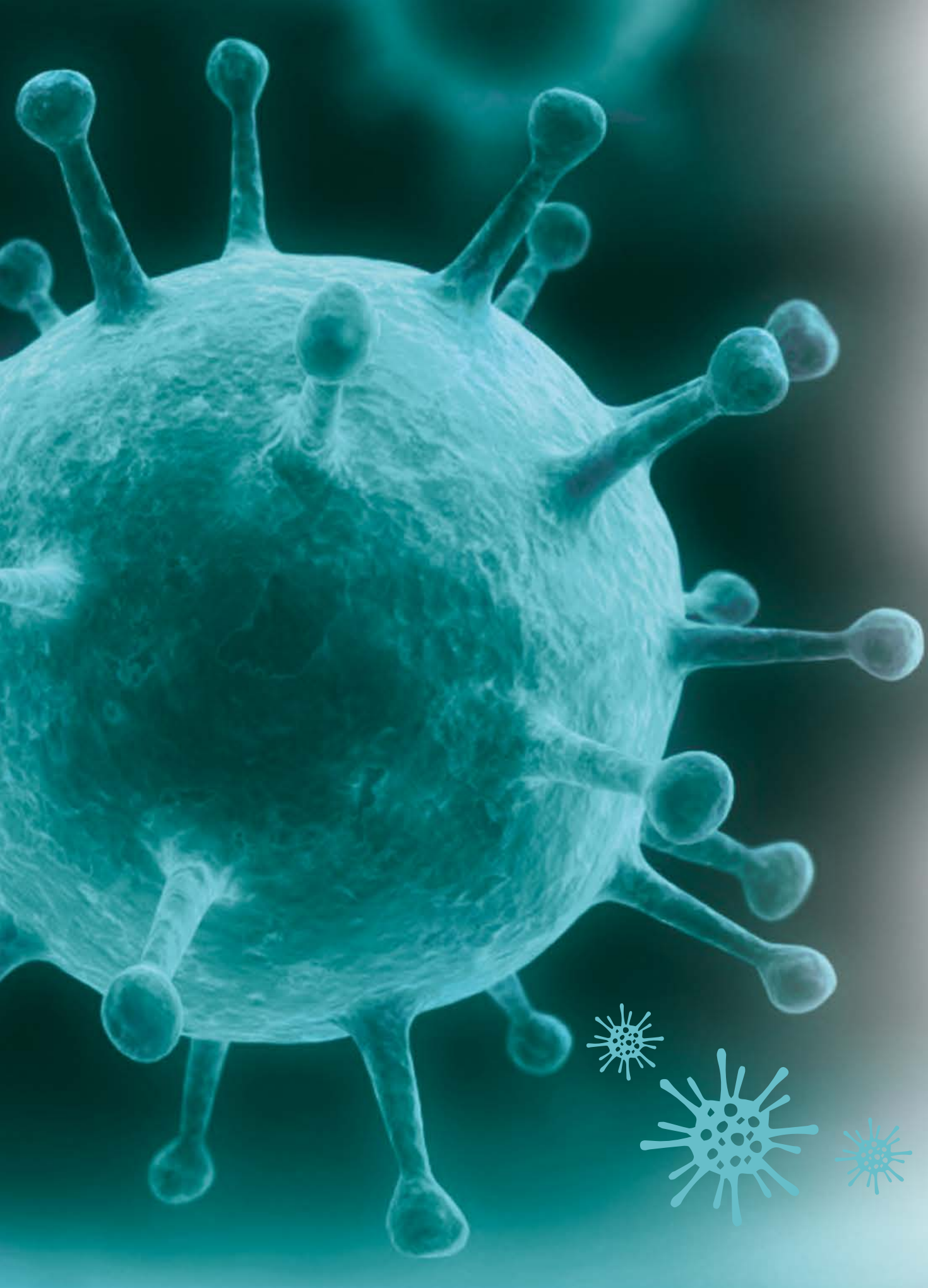
The aforementioned makes the presentation of this 2015 Memoir of the Institute of Health Carlos III a true pleasure as director; with respect, recognition and appreciation of the professionals that make each day a work of service to our fellow citizens.

Jesús Fernández Crespo
Director

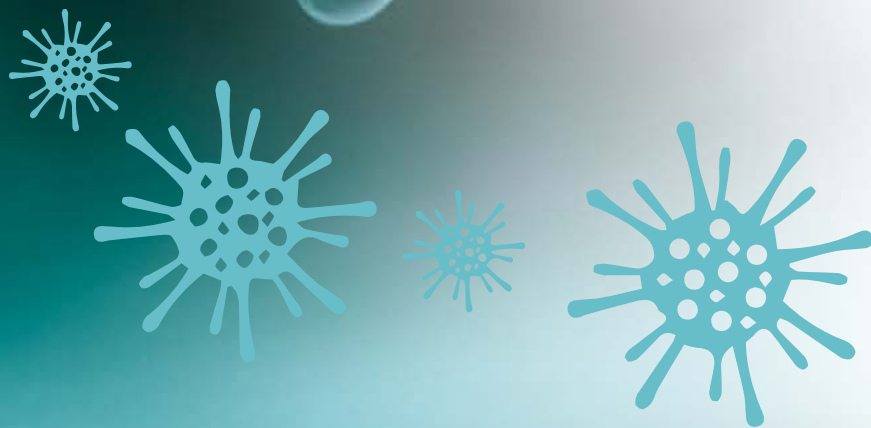
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Report 2015 Instituto de Salud Carlos III





1 Organization



1 Organization

1.1 Governing Bodies

The Carlos III Institute of Health is a Public Research Organization (PRO) with autonomous legal nature, which aims to develop and provide the highest quality scientific and technical services, directed towards the National Healthcare System (SNS in Spanish) as well as society as a whole.

In accordance with the Fifth Additional Provision of Royal Decree 345/2012, dated February 10th, which develops the basic organizational structure of the Ministry of Economy and Competitiveness, the Carlos III Institute of Health reports directly to the Ministry of Health, Social Services and Equality (MHSSE) for conducting implemented activities in health, planning and medical assistance fields; and in coordination with the Ministry of Economy and Competitiveness, through the Secretary of State for Research, Development and Innovation, for conducting applied research activities whenever they relate to the National Healthcare System (SNS).

The ISCIII associates with the SNS Research Centers so as to contribute to the structuring of research, certifies Health Research Institutes (IIS) and Cooperative Research Networks to focus research on the intended objectives and to promote excellence in research, as well as facilitate its own research resources.

1.2 Centers, Units, Schools and Foundations

The ISCIII Centers and Units, of national and international reference, develop research activities in biomedicine, environmental health and public health fields. Programs are designed for each research area to investigate diseases from a diagnostic, therapeutic and preventive standpoint in collaboration with multidisciplinary researchers and technologists. Their thematic priorities mainly include research towards infectious, chronic, rare, neurodegenerative, tropical and occupational diseases, in telemedicine, environmental health, epidemiology, and public health and healthcare.

The ISCIII also provides advanced scientific and technical services of national reference, with full incorporation of new technologies to improve health and social welfare.

These are oriented towards: reference laboratories, monitoring and alerting laboratories, scientific and technical training, health education, scientific information and documentation, assessment concerning transfer of research results, and evaluation of technologies and procedures applicable to clinical practice.

- National Microbiology Centre (CNM)
- National Epidemiology Centre (CNE)
- National Environmental Health Centre (CNSA)
- National Centre of Tropical Medicine (CNMT)
- Research Institute for Rare Diseases (IIER)
- Research Institute for Congenital Anomalies (CIAC)
- Telemedicine Research Unit
- Healthcare Research Unit (Investén-isciii)
- Functional Unit for Research into Chronic Diseases (UFIEC)
- Biological Alert Laboratory Network (RE-LAB)
- Agency for Evaluation of Healthcare Technology (AETS)
- National Library of Health Sciences (BNCS)
- UCM-ISCIII Joint Centre for Research on Human Evolution and Behavior

Schools

Through the National School of Public Health and the National School of Occupational Medicine, the ISCIII, without prejudice to the competences of other public bodies, conducts training, development and specialization for both medical and non-medical staff, in the fields of health administration and management, as well as the development of methodological, social and economic science disciplines applied to health.

Foundations

The following Foundations are ascribed to the Carlos III Institute of Health:

National Cancer Research Centre (CNIO), National Centre for Cardiovascular Research (CNIC) and the National Centre for Research on Neurodegenerative Diseases (CIEN), developing activities respectively in cancer, cardiovascular and neurodegenerative disease research areas.

1.3 Human Resources

In 2015, the same trend of recent years can be seen in a continued decline of ISCIII's own staff. The total number of personnel is 962 and the composition of the staff is made up of 556 civil servants, 192 permanent employees and 214 temporary employees (205 of them associated to projects).

The functional distribution is as follows: 161 scientists, 289 technologists, 178 research support personnel and 334 management personnel.

Instituto de Salud Carlos III

Personell Evolution		2011/2015															% Evolution
		2011			2012			2013			2014			2015			2011-2015
2011/2015		♀	♂	Total	♀	♂	Total	♀	♂	Total	♀	♂	Total	♀	♂	Total	%
Civil Servants	A1/G1	167	130	297	166	123	289	167	124	291	165	124	289	164	117	281	-5,39
	A2/G2	79	24	103	76	24	100	71	23	94	71	21	92	68	20	88	-14,56
	C1/G3	105	25	130	97	26	123	93	25	118	91	23	114	91	21	112	-13,85
	C2/G4	81	21	102	76	23	99	71	20	91	63	19	82	55	17	72	-29,41
	E/G5	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	0,00
	Total...	433	202	635	416	198	614	403	194	597	391	189	580	379	177	556	-12,44
Permanent Personnel	A1/G1	12	1	13	12	1	13	10	1	11	10	1	11	9	0	9	-30,77
	A2/G2	4	0	4	4	0	4	4	0	4	4	0	4	4	0	4	0,00
	C1/G3	70	27	97	65	26	91	64	25	89	62	25	87	59	24	83	-14,43
	C2/G4	34	13	47	33	13	46	33	13	46	28	11	39	27	7	34	-27,66
	E/G5	53	19	72	50	18	68	50	17	67	47	18	65	45	17	62	-13,89
	Total...	173	60	233	164	58	222	161	56	217	151	55	206	144	48	192	-17,60
Temporary Personnel	A1/G1	124	50	174	130	40	170	113	41	154	107	38	145	112	37	149	-14,37
	A2/G2	15	2	17	13	2	15	8	4	12	6	3	9	4	3	7	-58,82
	C1/G3	85	17	102	77	7	84	59	7	66	58	6	64	51	5	56	-45,10
	C2/G4	2	0	2	2	0	2	1	0	1	1	0	1	1	0	1	-50,00
	E/G5	2	2	4	4	2	6	4	2	6	1	2	3	0	1	1	-75,00
	Total...	228	71	299	226	51	277	185	54	239	173	49	222	168	46	214	-28,43
	834	333	1167	806	307	1113	749	304	1053	715	293	1008	691	271	962	-17,57	
Total	1167			1113			1053			1008			962			-17,57	
	2011			2012			2013			2014			2015				

Personnel Types	Total	Gender	Partial
Civil Servant	556	♀	379
		♂	177
Permanent Personnel	192	♀	144
		♂	48
Temporary Personnel	214	♀	168
		♂	46
	962		

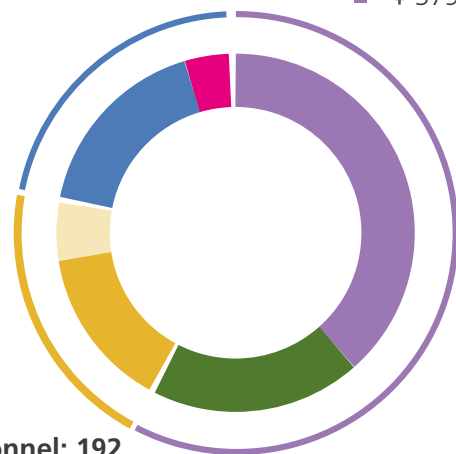
Personnel Types	Total	Gender	Partial
Scientific Personnel	161	♀	94
		♂	67
Technological Personnel	289	♀	226
		♂	63
Research Support Personnel	178	♀	137
		♂	41
Management Personnel	334	♀	234
		♂	100
	962		962

1

22%

Temporary Personnel: 214

- ♂ 46 = 5%
- ♀ 168 = 18%



20%

Permanent Personnel: 192

- ♂ 48 = 5%
- ♀ 144 = 15%

58%

Civil Servants: 556

- ♂ 177 = 18%
- ♀ 379 = 39%

18%

Research Support Personnel : 178

- ♂ 41; 4%
- ♀ 137; 14%

35%

Management Personnel : 334

- ♂ 100; 10%
- ♀ 234; 24%

30%

Technical Personnel: 289

- ♂ 63; 7%
- ♀ 226; 24%

17%

Scientific Personnel : 161

- ♂ 67; 7%
- ♀ 94; 10%

1.4 Economic Resources

1.4.1 Approved budget for the 2015 financial year

The credit approved for ISCC for the 2015 fiscal year was **273,820.83** euros, which is lower than the budget approved in the 2014 fiscal year by **12,942.01** euros (down by- 4,51%.)

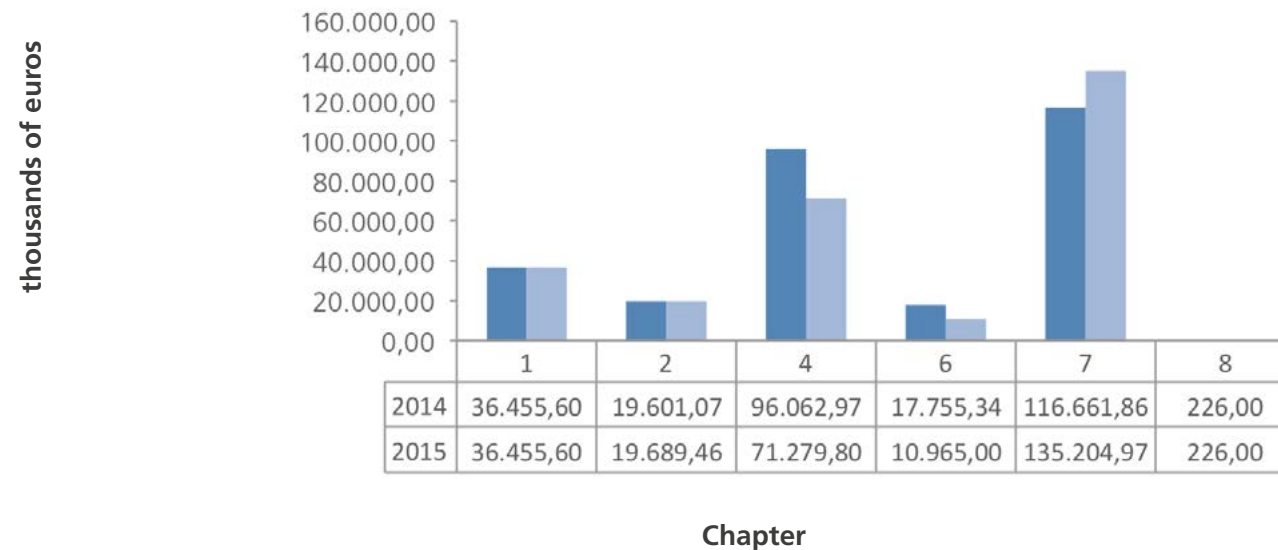
The distribution by chapters is as follows:

EXPENDITURE (in thousands of euros)

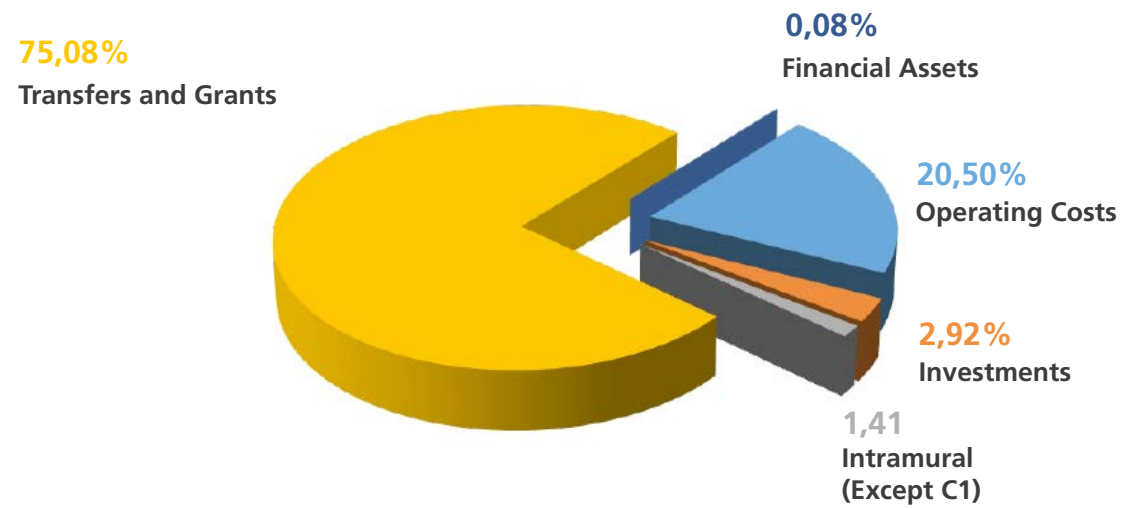
Chapter	2014	2015	Difference	%
1 Personnel Costs	36.455,60	36.455,60	-	-
2 Current expenditure on goods and services	19.601,07	19.689,46	88,39	0,45
4 Current transfers	96.062,97	71.279,80	-24.783,17	-25,80
6 Real investments	17.755,34	10.965,00	-6.790,34	-38,24
7 Capital transfers	116.661,86	135.204,97	18.543,11	15,89
8 Financial Assets	226,00	226,00	-	-
TOTAL	286.762,84	273.820,83	-12.942,01	-4,51

1

2015 Budget Expenses Comparative Statement

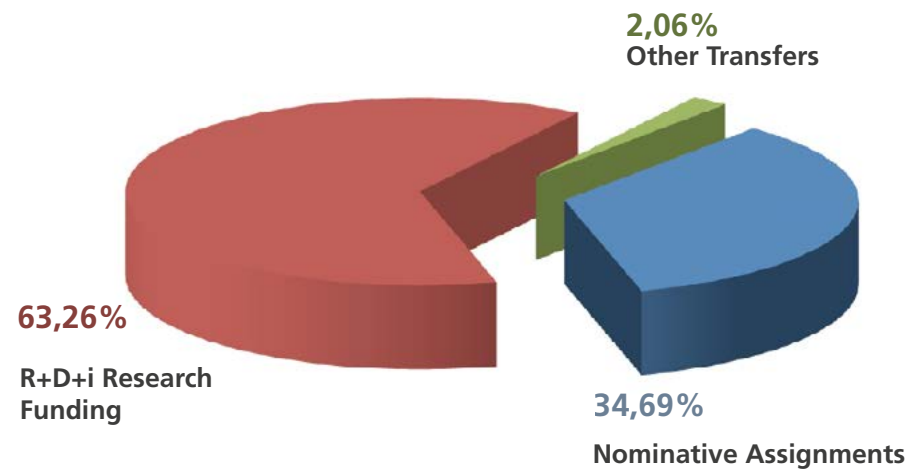


2015
Budget Expense Distribution

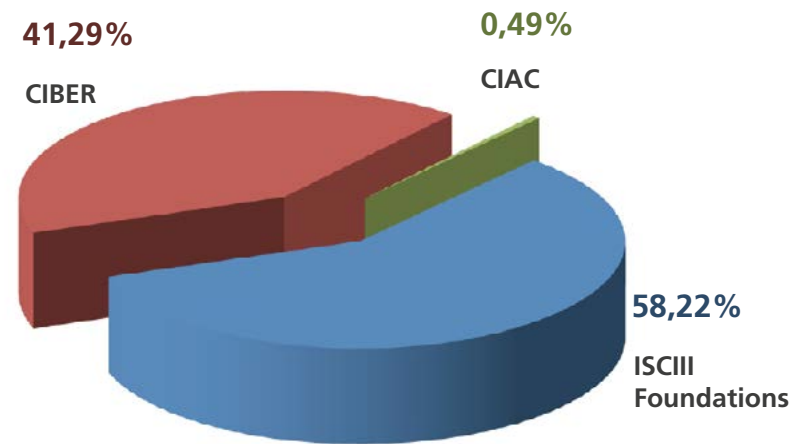


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2015 Budget EXPENSES
Distribution of transfers and grants



2015 Budget EXPENSES
Distribution of nominative assignments



INCOME

(in thousands of euros)

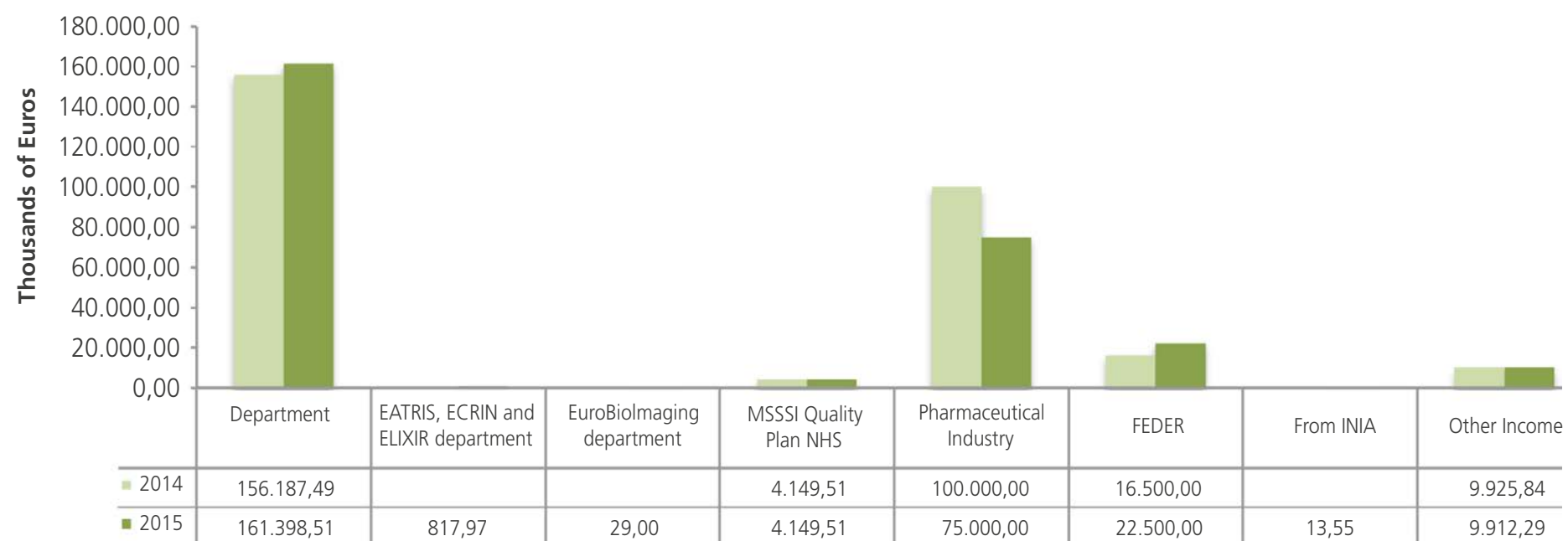
Source	2014	2015	Difference	%
Department	156.187,49	161.398,51	5.211,02	3,34
EATRIS, ECRIN and ELIXIR department	817,97	817,97		
EuroBioImaging department	29,00	29,00		
MSSSI Quality Plan NHS	4.149,51	4.149,51	-	-
Pharmaceutical Industry	100.000,00	75.000,00	-25.000,00	-25,00
FEDER	16.500,00	22.500,00	6.000,00	36,36
From INIA		13,55	13,55	
Other Income	9.925,84	9.912,29	-13,55	-0,14
TOTAL	286.762,84	273.820,83	-12.942,01	-4,51

The appropriations proposed in the Expenditure Statements are financed 58.94% with transfers from the Department and 27.39% with revenues derived from the execution of provisions of the Sixth Additional Disposition of Law 29/2006, dated July 26th, referring to warranties and rational use of medicines and health products.

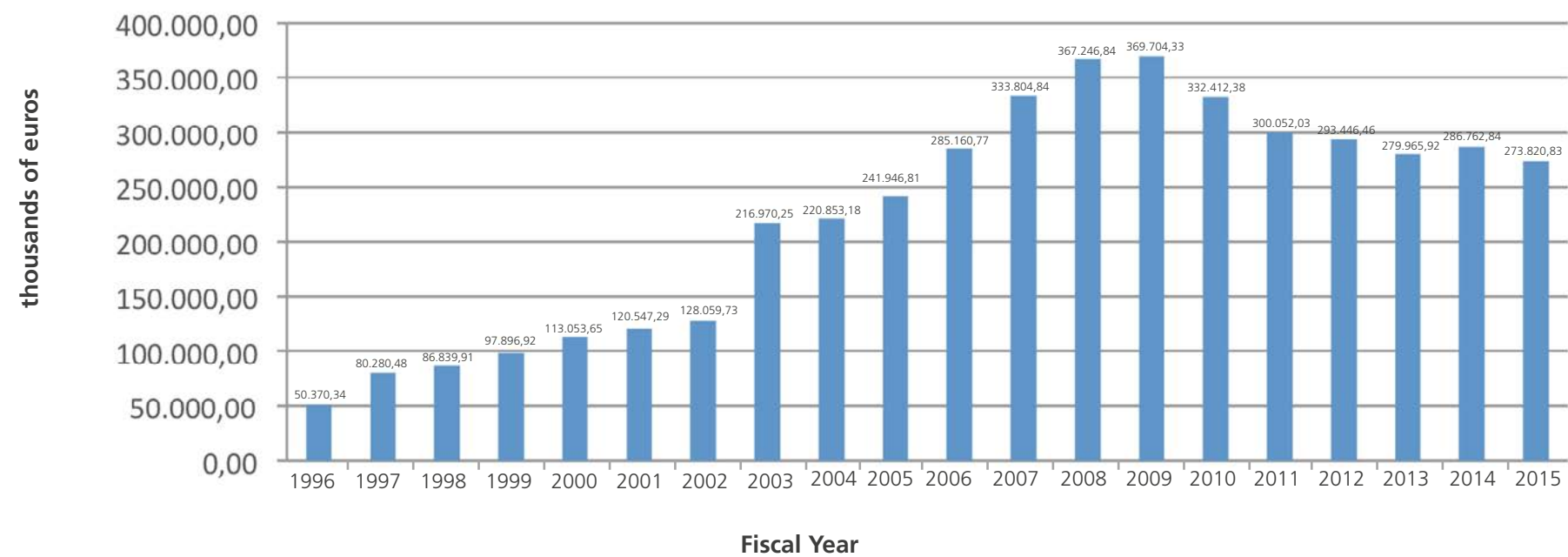
Lastly, the evolution of this organizations approved budget from 1996 to 2015 is as shown below:

1

2015 BUDGET INCOME Comparative Statement



INSTITUTE OF HEALTH CARLOS III
Approved budget evolution 1996 -2015





**Research and
Innovation
Activity
Management**

2

2 Research and Innovation Activity Management

The Carlos III Institute of Health is the Public Research Organization (OPI) that promotes, manages and evaluates and finances biomedical research in Spain through the Strategic Action in Health (AES in Spanish) in the framework of the 2013-2016 National Plan for Scientific and Technical Research and Innovation.

2.1 Strategic Action in Health 2013-2016

The National Plan for Scientific and Technical Research and Innovation for the 2013-2016 period (hereinafter the National Plan for R&D&I) includes four National Programs, displayed in Sub-programs and two Strategic Actions that are integrated into the fourth identified program: the National Program for R&D&I, Oriented to the Challenges in Society.

The Challenge in Health, Demographic Change and Welfare, fully aligned with Horizon 2020, includes, as a programmed action with a specific characteristic, the Strategic Action in Health 2013-2016, which aims to contribute to promote health and welfare for citizens and to develop preventive, diagnostic, healing, rehabilitation and palliative care for diseases, reinforcing and increasing the international competitiveness in R&D&I of the National Health System (SNS in Spanish) and other related companies in the sector, striving to position Spain in a forefront scenario where health acts as a fundamental axis for economic and social development.

In order to achieve these objectives, the AES proposes a set of complementary instrumental actions and synergies that fall within the National Sub-Programs for Training and Incorporation of the State Program for the Promotion of Talent and its Employability and within the State Sub-Programs for Institutional Strengthening and Knowledge Generation, of the National Program for Fostering Excellence in Scientific and Technical Research within the National Plan for R&D&I. Each of the subprograms is coordinated through one or various actions.

The following have been developed under the AES 2015 summon:

2.1.1 National Program for the Promotion of Talent and its Employability

2.1.1.1 National Sub-Program for Training:

- i-PFIS Contracts: IIS- Enterprise Doctorates in Health Sciences and Technology
- Training aids for health research management (FGIN)
- Río Hortega Contracts

2.1.1.2 National Sub-Program for Incorporation:

- IIS contracts for health research management
- Miguel Servet contracts types I and II
- Sara Borrell contracts
- Juan Rodés contracts
- Contracts for increasing research activity in the National Health System (SNS)

2.1.1.3 Subprograma Estatal de Movilidad:

- Mobility aids for research staff

2.1.2 National Program for Fostering Excellence in Scientific and Technical Research

2.1.2.1 National Sub-Program for Knowledge Generation

- Proyectos integrados de excelencia en los IIS
- Proyectos de desarrollo en medicina personalizada
- Proyectos de investigación en salud
 - A. Proyectos de investigación en salud
 - B. Proyectos de desarrollo tecnológico en salud
- Acciones complementarias de programación conjunta internacional

2.1.2.2 National Sub-Program for Knowledge Generation

- Incorporation of new groups to the CIBER Consortium

AES announcement novelties in 2015 include the introduction of aids towards Development Projects in Personalized Medicine and Incorporation of new CIBER Consortium Group, and some variations in the National Subprogram for Mobility aids.

The ISCIII is the managing body of the activities derived from the AES, executed through a unique competitive summon and the General Department of Development, Evaluation and Research (SGEFI) of the ISCIII is the body responsible for instructing proceedings.

2.1.3 AES proceedings in regards to the National Program for the Promotion of Talent and its Employability.

2.1.3.1 National Sub-Program for Training:

In 2015, the second promotion of the i-PFIS, ISS-Enterprise in Science and Health Technologies doctorates was convened. This is an aid aimed towards public-private collaboration through the development of training programs in business workplaces as well as accredited ISS. The distribution made by the CCAA has been as follows:

Autonomous Region	I-PFIS 2015						
	Approved Applications			Financed			Amount (€)
	F	M	T	M	H	T	
Andalusia	6	0	6	2	0	2	164.800
Aragon	1	0	1	1	0	1	82.400
Catalonia	6	4	10	1	2	3	247.200
R. of Valencia	2	2	4	0	1	1	82.400
Galicia	2	1	3	1	1	2	164.800
Madrid	4	4	8	0	2	2	164.800
TOTAL	24	12	36	5	6	11	906.400

F=Female | M=Male | T=total

These amounts correspond to the total duration of the aid, which entails 20,600 euros per year and a continuity of four years.

In regards to the aids for Health Research Management Training (FGIN), out of the 23 successful applications that were admitted, 10 were granted, each with a financial envelope of 20,000 euros per year with a three-year duration.

Rio Hortega contracts, aimed towards professionals who have passed the specialized medical training:

Autonomous Region	Rio Hortega 2015						
	Approved Application			Financed			Amount (€)
	M	H	T	M	H	T	
Andalusia	24	13	37	4	3	7	376.124
Aragon	2	1	3	0	1	1	53.732
Canary Islands	1	1	2	0	1	1	53.732
Cantabria	2	2	4	0	1	1	53.732
Castille and Leon	4	1	5	1	0	1	53.732
Catalonia	41	22	63	14	5	19	1.020.908
R. of Valencia	10	6	16	2	2	4	214.928
Galicia	12	2	14	4	1	5	268.660
Madrid	33	18	51	7	4	11	591.052
Navarra	3	2	5	1	0	1	53.732
TOTAL	132	68	200	33	18	51	2.740.332

The overall economic endowment of each contract is of 26,866 euros per year with a two-year duration.

2.1.3.2 National Sub-Program for Incorporation:

The second promotion of contracts for Health Research Management in accredited IISS (GIS) was convened. They are aimed towards managers who develop their activity performing activities that support the R+D+I management in the accredited IIS:

Autonomous Region	GIS 2015						
	Approved Applications			Financed			
	M	H	T	M	H	T	Amount (€)
Andalusia	1	1	2	1	0	1	80.598
Cantabria	2	0	2	1	0	1	80.598
Catalonia	2	0	2	1	0	1	80.598
Galicia	1	0	1	1	0	1	80.598
Murcia	1	0	1	1	0	1	80.598
TOTAL	7	1	8	5	0	5	402.990

The overall economic endowment of each contract is of 26,866 euros per year with a three-year duration.

The Miguel Servet Type I contracts are aimed towards doctors that have an accredited research track record in SNS centers, and are complemented by a research project with a duration of three years.

CC AA	Miguel Servet tipo I 2015						
	Approved Applications			Financed			
	M	H	T	M	H	T	Amount (€)
Andalusia	13	12	25	3	6	9	2.776.049,50
Canary Islands	2	1	3	0	1	1	324.000,00
Catalonia	17	11	28	4	3	7	2.260.850,00
R. of Valencia	10	4	14	2	1	3	850.000,00
Galicia	6	5	11	0	2	2	648.000,00
Madrid	17	8	25	4	1	5	1.620.000,00
Navarra	2	1	3	0	1	1	324.000,00
Rioja	1	1	2	1	1	2	648.000,00
TOTAL	68	43	111	14	16	30	9.450.899,50

Each contract has an economical endowment of 40,500 euros per year with a five-year duration.

The Miguel Servet type II contracts are aimed towards doctors that find themselves in their last year of execution of a Miguel Servet contract.

Autonomous Region	Miguel Servet tipo II 2015						
	Approved Applications			Financed			
	M	H	T	M	H	T	Amount (€)
Andalusia	0	2	2	0	2	2	182.250
Catalonia	10	2	12	9	2	11	1.053.000
R.of Valencia	2	1	3	2	0	2	182.250
Galicia	2	0	2	2	0	2	192.375
Madrid	3	1	4	2	1	3	293.625
Navarra	1	1	2	1	1	2	192.375

The economical endowments of these contracts is of 20,500 or 45,000 euros in their first year and are co-financed in the following years by 75% and 50%, and have a three- year duration.

The Sara Borrell contracts are aimed towards doctors who are recent graduates.

Autonomous Region	Sara Borrell 2015						
	Approved Applications			Financed			
	M	H	T	M	H	T	Amount (€)
Andalucía	24	10	34	0	1	1	80.598
Cantabria	3	0	3	1	0	1	80.598
Castilla and León	2	2	4	0	1	1	80.598
Catalonia	40	20	60	7	7	14	1.128.372
R. of Valencia	8	1	9	5	0	5	402.990
Madrid	22	11	33	4	1	5	402.990
Navarra	2	0	2	1	0	1	80.598
Rioja	1	0	1	1	0	1	80.598
TOTAL	102	44	146	19	10	29	2.337.342

The economical endowments of these contracts are of 26,866 euros per year and have a three-year duration.

The Juan Rodés contracts are aimed towards medical staff that has previously completed a Rio Hortega contract. They are performed in NHS (SNS in Spanish) that are part of an accredited ISS.

Autonomous Region	Juan Rodés 2015						
	Approved Applications			Financed			
	M	H	T	M	H	T	Amount (€)
Andalusia	6	0	6	4	0	4	540.000
Aragon	1	1	2	1	1	2	270.000
Catalonia	10	1	11	7	1	8	1.080.000
R. of Valencia	1	0	1	1	0	1	135.000
Madrid	8	2	10	6	1	7	945.000
Basque Country	0	2	2	0	1	1	135.000
TOTAL	26	6	32	19	4	23	3.105.000

Each contract has an economical endowment of 45,000 euros per year and a three-year duration.

The contracts for the Intensification of Research Activity in the NHS (SNS in Spanish) are aimed towards recruiting medical specialists or registered nurses to conduct part of the clinical activity of professional assistance while they develop research activities.

Autonomous Region	Intensification 2015						
	Approved Applications			Financed			Amount (€)
	M	H	T	M	H	T	
Andalusia	3	17	20	1	11	12	360.000
Aragon	3	2	5	2	1	3	90.000
Asturias	0	3	3	0	3	3	90.000
Canary Islands	0	4	4	0	2	2	60.000
Cantabria	0	4	4	0	3	3	90.000
Castille and Leon	1	5	6	1	1	2	60.000
Castille-La Mancha	0	2	2	0	2	2	60.000
Catalonia	8	30	38	4	20	24	720.000
R. of Valencia	4	8	12	1	2	3	90.000
Galicia	1	6	7	1	3	4	120.000
Madrid	5	31	36	3	20	23	690.000
Murcia	1	3	4		1	1	30.000
Navarra	3	2	5	1	2	3	90.000
Basque Country	4	4	8	2		2	60.000
TOTAL	33	121	154	16	71	87	2.610.000

The economical endowment of each contract is of 30,000 euros per year for medical staff and 15,000 euros per year for nursing staff.

2.1.3.3 National Sub-Program for Mobility:

The purpose of these aids is for financing stays with two modalities. The mobility of health professionals and researchers in the SNS (M-BAE) and new this year, the mobility of researchers hired under the AES (M-AES), aimed towards contracted PFIS, Rio Hortega, Juan Rodes and Miguel Servet Type I and II.

M-BAE

Autonomous Region	M-BAE 2015						
	Approved Applications			Financed			Amount (€)
	M	H	T	M	H	T	
Andalusia	3	2	5	2	1	3	35.000
Aragon	0	2	2	0	1	1	7.000
Canary Islands	0	1	1	1	2	3	42.000
Cantabria	0	0	0	0	1	1	21.000
Castille-La Mancha	0	2	2	0	2	2	35.000
Catalonia	6	12	18	4	8	12	150.500
R. of Valencia	2	3	5	1	2	3	31.500
Madrid	7	4	11	4	3	7	92.500
Murcia	1	1	2	0	1	1	21.000
Navarra	2	1	3	0	1	1	17.500
Basque Country	1	1	2	1	1	2	21.000
TOTAL	22	29	51	13	23	36	474.000

M-AES

Autonomous Region	M-AES 2015						
	Approved Applications			Financed			Amount (€)
	M	H	T	M	H	T	
Andalusia	3	2	5	3	2	5	48.000
Aragon	1	1	2	1	1	2	12.000
Catalonia	10	3	13	6	2	8	62.000
R.of Valencia	3	0	3	1	0	1	8.000
Madrid	4	0	4	3	0	3	16.000
Basque Country	0	2	2	0	1	1	6.000
TOTAL	21	8	29	14	6	20	152.000

The economical endowment of both aids is of 2,500 euros per month when the recipient is a Spanish center and 3,500 euros per month when it is foreign. The duration period is between two and six months.

Therefore, 314 new contracts will be formalized, which will include a total funding of 24,272.84 thousand euros.

2.1.4 AES PROCEEDINGS IN REGARDS TO THE NATIONAL PROGRAM FOR FOSTERING EXCELLENCE IN SCIENTIFIC AND TECHNICAL RESEARCH

2.1.4.1 NATIONAL SUB-PROGRAM FOR KNOWLEDGE GENERATION

Within the sub-program for Knowledge Generation, aids were summoned for Integrated Projects of Excellence (PIE); Development Projects in Personalized Medicine (PMP); Health Research Projects in two categories: Health Research Projects (PI) and Research Projects for Technology Development in Health (DTS); as well as Complementary Actions for international joint programming (AC)

The following summarizes the total data of the National Sub-Program for Knowledge Generation.

Granted amounts and success rates

Aid	Requested	Approved	Granted	% Success	Amount (in thousands of euros €)
PI	1.777	1.724	610	35,38	61.426,20
PIE	44	44	13	29,55	6.787,00
DTS	141	136	31	22,79	2.396,86
AC	79	79	30	37,97	2.618,12
PMP	24	24	5	20,83	4.428,07

2.1.4.1.1 INTEGRATED PROJECTS OF EXCELLENCE

The purpose of this aid was to finance research projects with innovative approaches and methods of proven quality, that represent a significant advance in the field of research in science and health technologies in accredited IIS.

Companies or other public or private entities interested in the development and results thereof should be linked to the projects.

The total number of applications received was 44 and 13 were awarded aids amounting to 6,787.00 thousand euros.

2.1.4.1.2 DEVELOPMENT PROJECTS IN PERSONALIZED MEDICINE

The purpose of this aid was to finance research projects of outstanding quality in personalized medicine, based on preliminary experiences that generate tangible benefits for patients and provide evidence for its implementation into the NHS (SNS in Spanish) and health authorities.

The projects were to be coordinated and developed by several multidisciplinary research groups, being able to belong to different scientific institutions.

24 applications were received and 5 were funded, amounting to a total of 4,428.068 thousand euros.

2.1.4.1.3 HEALTH RESEARCH PROJECTS

The purpose of this aid was financing projects in one of the following modalities:

- *Health research projects*. Projects of outstanding quality, whose main objectives were: a) the transfer and application of scientific and technical knowledge towards improving prevention, diagnosis and treatment of diseases and advocacy of public health and health services; b) promote synergies, further talent and employability and strengthen governance structures that add scientific technical capabilities to the SNS assistance centers.

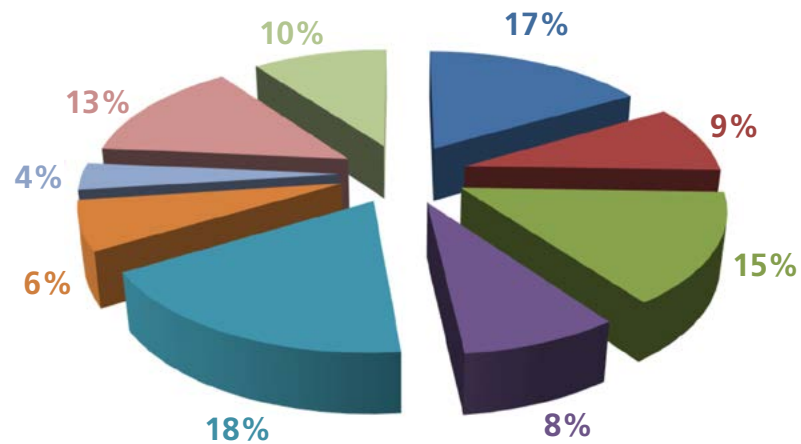
1,724 applications were received and 610 were funded, amounting to a total of 61,426.202 thousand euros.

The communities with the highest number of applications were Cataluña (32,19%), Madrid (21,75%) and Andalucía (14,32%).

- *Technological development in health projects*. Projects based on preliminary experiences that have been contrasted, impelling them in their development phase.

136 applications were received and 31 were financed, amounting to a total of 2,396.86 thousand euros.

2015 Financing of Health Research Projects by Areas



18%
Epidemiology, Public and Occupational Health

6%
Pediatrics, Perinatal Med., Congenital and Metabolic Anomalies

4%
Bioengineering and Genomic Technologies

13%
Chronic, Inflammatory, Nephrological and Respiratory Diseases

10%
Endocrine and Digestive Diseases, Surgery

17%
Cancer

9%
Cardiovascular Diseases

15%
Neurological Diseases and Mental Disorders

8%
Infectious Diseases and AIDS



2.1.4.1.4 COMPLEMENTARY ACTIONS THROUGH JOINT INTERNATIONAL PROGRAMMING (AC)

The purpose of this action was to fund international joint programming health research projects, in the framework of transitional consortia, in which the ISCII is committed to supporting relevant collaborative projects, where Spanish teams participate with teams from other countries.

The international summons of concurrency in the framework of the complementary actions have been:

- **JPco-fuND:** "ERA-Net for Establishing synergies between the EU Joint Programming Initiative on Neurodegenerative Disease Research, in particular Alzheimer (JPND), and Horizon 2020".
- **Transcan 2:** "ERA-Net for Translational Cancer Research".
- **E-Rare 3:** "ERA-Net for Research Programs on Rare Diseases".
- **ERACoSysMed:** "Collaboration on systems medicine funding to promote the implementation of systems biology approaches in clinical research and medical practice".
- **NEURON-II:** "European Network for Neuroscience Research Funding".
- **Euronanomed-II:** "EUROPEAN Network for translational collaborative RTD projects in the field of NANOMEDICINE".

79 applications were received and 30 were funded, amounting to a total of 2,618.117 thousand euros.

Table. N° of groups and researchers that participate in European programs

Program	N° Groups	N° Researchers
ERACOSYSMED	3	14
ERANET-LAC	7	45
E-RARE	4	15
EURONANOMED	4	23
INFECT-ERA	1	1
JPND	1	4
NEURON	3	8
TRANSCAN	7	43
TOTAL	30	153

Table. Distribution of aids granted by Autonomous Region

Autonomous Region	PI		AC		PMP		PIE		DTS	
	Nº Aids	Amount (€)	Nº Aids	Amount (€)	Nº Aids	Amount (€)	Nº Aids	Amount (€)	Nº Aids	Amount (€)
ANDALUSIA	65	6.435.234	3	166.375					5	284.570
ARAGON	12	940.110								
ASTURIAS	7	509.410							1	89.100
BALEARIC ISLANDS	9	615.890								
CANARY ISLANDS	6	366.267	2	131.043						
CANTABRIA	7	879.670					2	809.325	1	67.100
CASTILLE - LA MANCHA	8	724.185								
CASTILLE AND LEON	24	2.068.677							2	205.700
CATALONIA	233	24.960.055	13	1.356.191	3	2.641.539	4	2.233.550	7	634.150
REGION OF VALENCIA	26	2.462.955	4	254.153			1	589.050	4	269.500
EXTREMADURA	4	431.365	1	74.960						
GALICIA	24	2.276.918	1	19.965	1	980.306			2	156.200
MADRID	143	15.050.053	3	310.038	1	806.223	5	2.244.825	6	513.700
MURCIA	8	779.664					1	910.250		
NAVARRA	16	1.471.663	2	249.381					1	59.139
BASQUE COUNTRY	16	1.368.178	1	56.011					2	117.700
RIOJA	2	85.910								
TOTAL	610	61.426.202	30	2.618.117	5	4.428.068	13	6.787.000	31	2.396.859

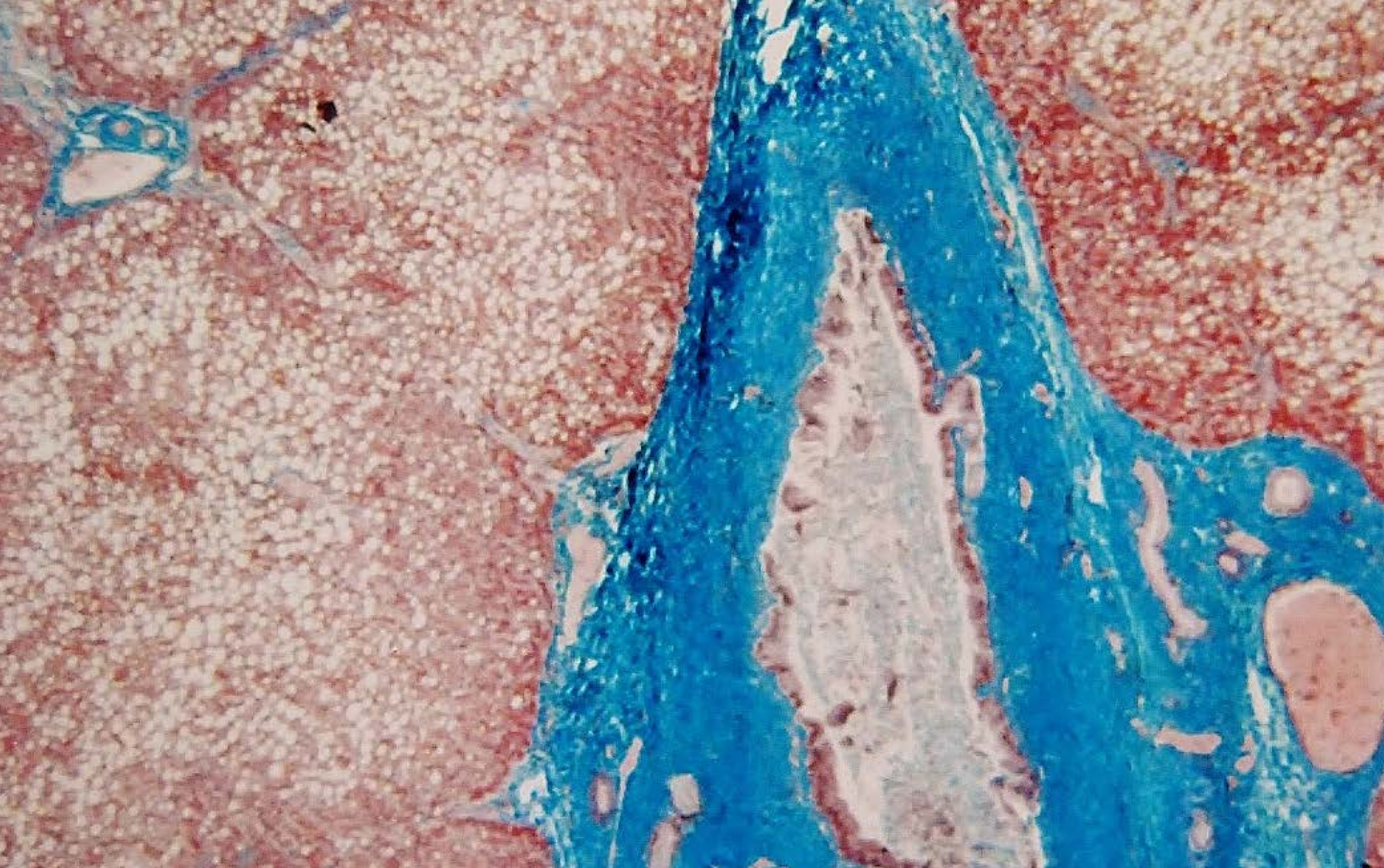
2.1.4.2 NATIONAL SUB-PROGRAMME FOR INSTITUTIONAL STRENGTHENING

Aids have been convened within the Institutional Strengthening sub-program to incorporate new CIBER Consortium groups. The purpose of this aid was to strengthen thematic areas of CIBER in specific descriptors and incorporate new relevant scientific groups.

132 applications were received and 11 were financed, amounting to a total of 703,350 euros.

Table. Distribution by areas of group incorporation into CIBER consortium

Subject Area	Groups	Amount (€)
Bioengineering, Biomaterials and Nanomedicine	1	65.000
Diabetes and Metabolic Diseases	1	65.000
Rare Diseases	2	130.000
Respiratory Diseases	1	65.000
Epidemiology and Public Health	2	128.250
Pathophysiology of obesity and nutrition	2	120.100
Mental Health	2	130.000
TOTAL	11	703.350



2.2 Biomedical Research Networking Centers (CIBER)

The ISCIII conducts coordination, evaluation, monitoring and promotion of the Biomedical Research Networking Centers (CIBER) that have been consolidated as public government consortiums with their own legal personality.

In 2015, the major CIBER milestones have been:

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www.ciberisciii.es

Area of Rare Diseases (CIBERER), has patented a new diagnostic method for idiopathic scoliosis and published the first catalog of genetic variation in the healthy Spanish population. In addition, CIBERER has applied for two patents for therapeutic uses, has obtained orphan drug designation of bazedoxifene

acetate as indicated in hereditary hemorrhagic telangiectasia (HHT) and has achieved the first National GMP room approved by the AEMPS for the development of protocols for gene therapy with hematopoietic stem cells. Highlights of its contribution include the development of clinical practice guidelines as a guide on Tuberous Sclerosis Complex (TSC) and Proper Clinical Practice Guidelines for Imprinting Diseases.

Area of Physiopathology of Obesity and Nutrition (CIBEROBN), the main lines of research have resulted in major publications. Studies have focused on the knowledge of the beneficial effects that the Mediterranean diet exerts on cognitive decline; in contributing to global adipose tissue lipolysis by modulating metabolic control, adipose expansion, insulin resistance and inflammation as well as the response to surgical and/or dietary interventions; and the relationship between nutrition and chronic diseases including obesity, cardiovascular disease, total mortality and causes and incidence of breast cancer.

Area of Bioengineering, Biomaterials and Nano medicine (CIBERBBN), has participated as a partner in the European Project DRIVE, in which new biomaterials and surgical devices that enhance transplantation and survival of insulin-producing pancreatic islets for the treatment of diabetes will be developed. Also highlighted is the “Functionalized Nano liposomes for the development of therapies for intracellular-based diseases. Application to Fabry disease and homozygous familial hypercholesterolemia” project, including economic investment on behalf of industrial partners.

Area of Epidemiology and Public Health (CIBERESP), has developed a collaborative project on “Effectiveness of the pertussis vaccine in pregnant women in their third trimester to prevent pertussis (whooping cough)” and has participated in meetings with experts that are aimed towards the adequacy of the vaccine immunization schedule. CIBERESP has also participated in the study of clinical care process (MAPAC), whose results modify clinical practice and are monitored through the digital Dianasalud platform (www.dianasalud.com), which includes recommendations for adopting the best clinical decisions.

Area of Mental Health (CIBERSAM), has increased the number of publications in the first quartile and has registered two patents. CIBERSAM has also participated in three new European projects and has presented and coordinates a roadmap for Mental Health Research in the European Parliament. Furthermore, CIBERSAM has fostered the first meeting between research, patients and families. Additionally, CIBERSAM has also initiated the first randomized clinical trial in Deep Brain Stimulation for treatment-resistant major depression.

Area of Diabetes and Associated Metabolic Disorders (CIBERDEM), has initiated the epidemiological fieldwork study Di@bet.es II in order to establish Type 2 Diabetes incidence in Spain, as well as the Project INFLAMES, in collaboration with CIBEROBN, CIBEREHD y CIBERESP to identify the mechanisms of chronic inflammatory processes in prevalent diseases such as type 2 diabetes and obesity, and to design new therapeutic strategies for treatment. The CIBERDEM has also participated in the second Endocrine Society Scientific Statement on endocrine disrupting chemical agents.

Area of Respiratory Diseases (CIBERES), has applied for a new patent. Among the most important milestones, significant changes in clinical practice due to the results obtained from a comparative study on the administration of corticosteroids and antibiotics in severe pneumonia were achieved. Furthermore, the candidate vaccine against tuberculosis, MTBVAC, successfully launched the Phase IB clinical trials in South Africa, and will be the first live attenuated vaccine of Mycobacterium tuberculosis to begin its testing on newborns. Additionally, CIBERES has also developed a predictive analysis that helps customize the most appropriate treatment for sleep apnea in patients with hypertension.

Area of Liver and Digestive Diseases (CIBEREHD), researchers have led international studies on the effectiveness of new treatments and have advised the MSSSI on the National Hepatitis Plan. Among the most important studies in 2015 are: “Minimal Hepatic Encephalopathy and Critical Flicker Frequency Are Associated with Survival of Patients with Cirrhosis” and “Identification of risk loci for Crohn’s disease phenotypes using a genome-wide association study”. In addition, four clinical practice guidelines in the field are highlighted.

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www.ciberned.es

The CIBER of Neurodegenerative Diseases has increased its collaboration with both international and national projects, actively participating in the activities of the Technical Committee of the Strategy in Neurodegenerative Diseases of the National Health System (SNS) and in the Working Group on Alzheimer’s Disease Genetics and dementias to continue the multicenter study of these diseases related in Spain as well as in the European Network for Multidisciplinary Research on Autophagy and its Translation in Biomedicine and Biotechnology. In addition, there have been four new clinical guidelines and 35 active clinical trials have been maintained.

Highlight articles published in 2015 have been:

CIBERES: Lange P, Celli B, Agusti A, BojeJensen G, Divo M, Faner R et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *NEngl J Med.* 2015; 373 (2):111-22. doi: 10.1056/NEJMoa1411532. PMID:26154786.

CIBERDEM:Marquard J, Otter S, Welters A, Stirban A, Fischer A, Eglinger J et al. Characterization of pancreatic NMDA receptors as possible drug targets for diabetes treatment. *Nat Med.* 2015; 21(4):363-72. doi: 10.1038/nm.3822. PMID: 25774850.

CIBERSAM: GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.*2015;385(9963):117-71. doi: 10.1016/S0140-6736(14)61682-2.PMID: 25530442

CIBEREHD: Alonso A, Domènech E, Julià A, Panés J, García-Sánchez V, Mateu PN, et al. Identification of risk loci for Crohn's disease phenotypes using a genome-wide association study.*Gastroenterology.* 2015 Apr;148(4):794-805. doi: 10.1053/j.gastro.2014.12.030. PMID: 25557950.

CIBERESP: Viale L, Allotey J, Cheong-See F, Arroyo-Manzano D, Mccorry D, Baggary M, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. *Lancet.* 2015 Nov 7;386(10006):1845-52. doi:10.1016/S0140-6736(15)00045-8.PMID: 26318519.

CIBERBBN: Inostroza-Brito KE, Collin E, Siton-Mendelson O, Smith KH, Monge-Marcet A, Ferreira DS, et al. Co-Assembly, spatiotemporal control and morphogenesis of a hybrid protein-peptide system. *NatChem.* 2015 Nov;7(11):897-904. doi: 10.1038/nchem.2349.PMID:26492010.

CIBEROBN: Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martínez-González MÁ, et al. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. *JAMA InternMed.* 2015 Jul;175(7):1094-103. doi: 10.1001/jamainternmed.2015.1668. PMID: 25961184.

CIBERER:Launay N, Aguado C, Fourcade S, Ruiz M, Grau L, Riera J, Guilera C, Giròs M, Ferrer I, Knecht E, Pujol A. Autophagy induction halts axonal degeneration in a mouse model of X-adrenoleukodystrophy.*ActaNeuropathol.* 2015 Mar;129(3):399-415.doi: 10.1007/s00401-014-1378-8 PMID: 25549970

CIBERNED: Gazulla J, Berciano J. Multiple-system atrophy. *N Engl J Med.* 2015; 372(14):1374-5. doi: 10.1056/NEJMc1501657#SA2. PMID: 25830436





2.3 Thematic Networks for Cooperative Research (RETICS)

The Thematic Networks for Cooperative Research in Health (RETICS in Spanish) are organizational structures composed by the association of variable sets of biomedical research centers and groups, of multidisciplinary character, that report to different public or private administrations and belong to a minimum of four Autonomous Regions, with the general objective of promoting collaboration between NHS research groups that work on related topics and, at the same time, facilitate the structuring of the research that is being developed.



MOTHER-CHILD HEALTH AND DEVELOPMENT NETWORK (SAMID) -RD12/0026

Web Address: <http://www.redsamid.net/>

The most important milestones have been on behalf of the obstetrical equipment: (i) prematurity prevention; (ii) methods for detection of intrauterine growth retardation and, (iii) evaluation of fetuses with intrauterine disease. In neonatology: (i) validated tools for detecting predictive signs of neurological damage by image; (ii) biomarkers of oxidative stress in resuscitation, respiratory pathology as well as neurological; (iii) prototype of human milk pasteurizer (iv) experimental and clinical models of toxics in perinatal period. Experimental models of

cardiac arrest resuscitation in the post-neonatal age have been developed. An experimental course on animal studies in pediatrics has been organized. All of these contributions have been financed with national and international competitive grants and have been published in journals of impact.



RESEARCH NETWORK FOR INFLAMMATION AND RHEUMATIC DISEASES (RIER) – RD12/0009

Web Address: <http://www.red-rier.org>

In 2015, the RIER has achieved significant progress in the field of genetic stratification of rheumatoid arthritis, in relation to its different clinical forms, therapeutic responses and cardiovascular comorbidity. This progress is a result of three major multicenter cohorts established during RIERs trajectory in the previous year. There have also been significant advances in understanding the cellular and molecular pathology of arthritis, with translational projection in the prognosis and therapy of this disease.

In 2015, the groups within the network launched 10 new clinical trials and published 6 clinical practice guidelines, 3 of them in collaboration with other groups in the network and 172 articles in refereed journals, of which 60% were in journals of the first quartile (FI total 872.25; FI average 5.1).

RESEARCH NETWORK IN HEALTH SERVICES ORIENTED TOWARDS CHRONIC DISEASES (REDISSEC) – RD12/0001

Web Address: <http://www.redissec.com/es>

REDISSEC has led 139 projects, 52 in collaboration with 2 or more network groups. Of the 52 collaborative projects, 12 are international and the rest are national, resulting in products such as publications (840 with the REDISSEC signature; en 114 of them have participated in 2 or more groups), reports, contracts and agreements, software and clinical practice guidelines. Similarly, the work carried out by the annual organization of REDISSEC sessions, with specific spaces for the REDISSEC communications in four national and international congresses, has been disseminated. The network is present in various international forums and consortia: in the B3 del EIP/AHA group, the Join Action CHRODIS, the Joint Action EUnetHTA II y III (namely, European Union Network for Health Technology Assessment), the MasterMind Project or WHO Europe (The European Observatory of Health Systems and Policies). The network has organized summons for mobility between network groups and international mobility. REDISSEC is developing a Diploma Course in Health Services Research and Chronicity as a training program for the network. In addition to its own website, REDISSEC promotes various platforms such as the RECH web (Spanish Network of Hospital Costs; <https://www.rechosp.org/rech/faces/es/jsf/index.jsp>), the CAMISS Project (Health Research Services in Breast cancer; <http://www.camiss.info/>), the PYDeSalud web (www.pydesalud.com) or the ATLAS of Medical Practice Variations (<http://www.atlasvpm.org/>).





CEREBRAL VASCULAR DISORDER NETWORK (ICTUS) (INVICTUS)

Web Address: <http://www.renevas.es>

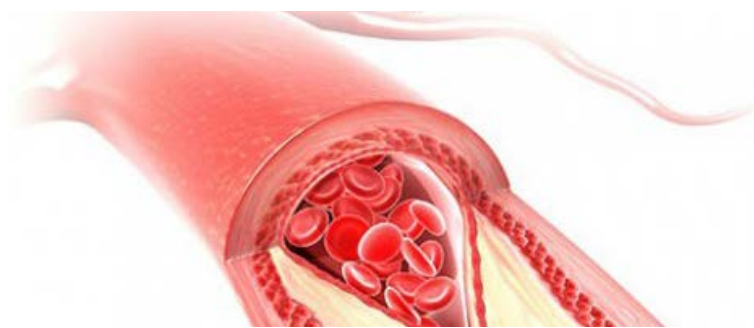
During 2015, the INVICTUS Network has accomplished significant collaborative research projects, highlighting two European projects coordinated within the H2020 program, in which several research networks participated, obtaining more than 14 million euros between the two.

The license has been obtained with a pharmaceutical company for the patents PCT/ES2011/070344; PCT/ES2011/070347; EP15382229, with which it has signed a contract for the completion of the pre-clinical study for the development of the rGOT as a systemic glutamate catcher.

A new pharmaceutical drug has been identified and validated (Code: CBG000592. Protected by patent: EP15382229.1) by the pharmaceutical drug repositioning strategy, with activity for reducing glutamate levels, similar to oxaloacetate and GOT and with neuro-protective effects in ischemia models.

A series of aptamers with agonist and antagonist activity for TLR4 (P201430955) have been patented, and have been licensed by a biotechnology company.

Of the many published articles, a special highlight due to its high impact index is noted: Chamorro et New Engl J Med. 2015.11;37 2 (24):2296-306 and Dávalos et Lancet Neurol 2015 14(6):575-84).



MULTIPLE SCLEROSIS NETWORK (REEM)– RD12/0032

Web Address: <http://www.reem.es/>

The principal milestones achieved by the Spanish Network of Multiple Sclerosis in 2015 are the identification of several biomarkers for MS (EM in Spanish):

Biomarkers for tracking and monitoring MS by determining levels of chitinase protein and oligoclonal bands of IgM in patient's cerebrospinal fluid. The development of image markers that use optical coherence for predicting clinical sequelae in patients with optic neuritis outbreaks.

These biomarkers are being implemented in most hospital in the NHS, and consequently can be used in monitoring patients with MS.



NETWORK FOR RESEARCH INTO INFECTIOUS DISEASES (REIPI) – RD12/0015

Web Address: <http://www.reipi.org>

In 2015 REIPI continued the development of its two research programs (anti-microbial resistance and antimicrobial use, and infection in transplant patients and other immunocompromised patients), with the idea of carrying out translational and international research, that determines health benefits through intervention studies capable of changing clinical practice, and the development of registered products which can later be exploited commercially. In total, 16 groups are actively developing more than 60 research projects in 2015, with objectives and topics ranging from basic research to randomized clinical trials. Sixteen of these projects were funded by international institutions, including 13 that have been funded by the European Union. In addition, 11 projects funded by private companies are being developed. Currently, 14 controlled randomized trials are being coordinated. Furthermore, several REIPI groups are leaders of the 3 COMBACTE consortia, funded by the Innovative Medicines Ini-

tiative (IMI; European Union and the EFPIA). This network also carries out the National Coordination of the European networks CLIN-NET, LAB-NET, STAT-NET and EPI-NET, also funded by the IMI, with the aim of performing innovative trials in infectious diseases in European countries, both academic as well as industry driven.

Network “news” was published on the 22 on the REIPI website and has received more than 6150 visits. During 2015, REIPI published 166 articles journals in the first quartile in function of their impact factor, out of which 75 are in the first decile; REIPI has participated in the publication of six guidelines or consensus documents, including one international publication. Moreover, the REIPI groups have registered 6 patents, several of these at an international level.



RED DE ENFERMEDADES OCULARES (OFTARED) - RD12/0034

Web Address: <http://www.oftared.com>

Worth noting as an organization, is the signing of agreements through patient associations (Spain Retina, Macula and Sjögren’s syndrome) with the CIBER of rare diseases and the Foundation of the Spanish Society of Ophthalmology. The annual meeting with the CIBER BBN and ER, Ophthalmology cluster companies (Cluster4Eye) and patient associations. Glaucoma sub programs with multicenter studies such as the express implant (Alcon Global), with a glaucoma diagnostic calculator or a guide for drug treatment. The retina sub program with the creation of the “Macula Spanish Club”, and three guides in collaboration with the SERV. In the eyepiece diopter with a guide and expansion of the ring and explanted lens collection (1098 of 23 centers), as well as multicentric databases. And in the ocular surface with a patent license. And a good number of publications with 4 in PRER, the journal with the highest impact index factor in the area that is only accessed by invitation.



RED DE CÁNCER (RTICC) – RD12/0036

Web Address: <http://www.rticc.org>

Among the most important activities and results, RTICC 2015 highlights include the signing of several cooperation agreements between the RTICC and various cooperative clinical groups specialized in diverse tumor diseases, GECP (lung cancer), SOLTI, GEICAM (breast cancer), GELTAMO, GETH, PETHEMA, CETLAM (hematologic tumors), as well as other cooperative research structures financed by the ISCII (CIBER and REDISSEC) and cancer research associations such as ASEICA.

Also worth mentioning within the RTICC Training and Mobility Program, is the granting of 48 training aids for a total value of 94,234.86€ (24 travel bags, 13 training rooms, 9 introduction to research scholarships and 2 aids for organization courses) as well as the celebration held in Pamplona on October 2015 for the V Scientific Meeting of Young Researchers of the RTICC, which relied on the participation of 63 RTICC researchers under 35 presenting 29 communications (12 oral and 17 in poster form).

In 2015, the groups affiliated to the RTICC have published a total of 950 articles, 3% more than the previous year, a third of which have a collaborative nature, with a notable increase in quality, reaching a total of 6,647 IF in 2015, with an average IF of 6,997, which represents 20% more than in 2014.

Finally, in relation to transfer results, the 28 guides and innovations in clinical practice developed by RTICC groups (45% collaborative) that affect the processes of prevention, diagnosis and treatment or care of patients, as well as the 546 active clinic trials in 2015 in which RTICC groups participate and the 6 patents applied for in 2015 are all worth noting.



RESEARCH NETWORK FOR ADVERSE REACTIONS TO ALLERGENS AND DRUGS (RIRAAF) -RD12/0013

Web Address: <https://chirimoyo.ac.uma.es/riraaf/>

New prototypes have been developed for studying the structure that results from the haptization of endogenous proteins by clavulanic acid, determining which are the anchor point of clavulanic acid in human albumin, observing that it expresses a differentiated haptization in respect to amoxicillin and benzyl penicillin. In NSAIDs (AINES in Spanish) a large number of cases have been published with immediate selective response to arylpropionics including ibuprofen and naproxen. In the case of hypersensitivity reactions to NSAIDs, non-described gene variants have been identified in the arachidonic acid pathway in patients with exacerbated respiratory disease.

A GWAS study was conducted for reactions to beta-lactams, finding significant associations with certain class II polymorphisms histocompatibility antigens.

The number of papers published by the RIRAAF is 16 original manuscripts and 6 reviews. Highlights include collaborations with ALK-Abella, Diater and Aleropharma, with which RIRAAF has contracts for Phase II testing or studies for product validation. Regarding applications for patents, two have been presented.



RED DE TRASTORNOS ADICTIVOS - RD12/0028

Web Address: <http://redrta.es/>

During 2015, the Addictive Disorders Network has continued to develop its scientific activity in the two integrated research projects on psychiatric comorbidity in cocaine addicts and on medical consequences of alcoholism. More than 200 scientific articles have been published in indexed journals, presenting more

than 250 papers, lectures or posters, fending 44 doctoral theses and establishing 30 collaborations with the business sector. As milestones of the Alcohol Program, highlights include registration of patients in treatment for alcohol use in a web platform cohort (CohRTA) and the identification of targets (ligands and receptors) such as lysophosphatidic acid (LPA1R), fractal kina (CX3CLR1), anandamine/2-AG (CB2), oleoylethanolamide (PPARalpha) for the diagnosis, prognosis and treatment of alcohol, as well as the role of natural immunity and the TLR4 receptor. Highlights in the Psychiatric Comorbidity in Patients Addicted to Cocaine Project include the multicenter studies published about the prevalence and characteristics of the addicted population that suffer comorbidity, and the identification and publication of reliable biomarkers of consumption, psychiatric severity and comorbidity (immunological, growth and endocannabinoid factors). A bioinformatics platform has been developed for candidate gene analysis in dual pathology (Psygenet) as well as an App for a screening interview of dual pathology in addictions for use by health professionals.



KIDNEY DISEASE NETWORK (REDINREN)

Web Address: <http://redinren.org/>

Identification of kinase linked to integrine (ILK) as a new biomarkers and therapeutic target in hypertension, diabetes and chronic kidney disease tissue damage.

Development of new drugs (hybrid losartan-antioxidant, new selective calpain inhibitors) with 4 national patents for kidney damage, three of them extended to an international level (PCT).

Completion of NEFRONA 4 year follow up study, the COSMOS European multicenter study (20 countries) of epidemiology of bone disease from kidney disease, and a multicentric, controlled and randomized independent clinical Trial (FIS EC 08/00055), in which three immunosuppression alternatives are compared for the prevention of Novo Diabetes post renal transplantation (EUDRACT: 2008-005617-22).

Development of the platform-viewer of Glomerular Pathology Bio banks.



NETWORK OF TROPICAL DISEASES (RICET)

Web Address: [http:// www.ricet.es](http://www.ricet.es)

Consolidation of the clinical-epidemiological network of imported tropical diseases which involved the participation of 27 centers of 8 CCAA (autonomous regions) with a total of 15,885 registered diagnostics of pathology imported by immigrants and travelers.

Development of Quantiferon-leishmania for studying leishmaniasis outbreaks in Spain and their applicability in clinical trials and in the monitoring of immunocompromised patients.

Development of a set of tools for an impact analysis model of climate and global change.

Development of diagnostic tools for arbovirus (Dengue, Zika and Chikungunya) and molecular markers for their vectors (i) Aedes de virosis, (ii) Bulinus for Schistosomiasis, (iii) Lymnaeas for Fascioliasis, and (iv) Triatominos of the Chagas Disease.

Biomarkers for the Chagas Disease pathology have been identified and developed, which have a different phenotypic and functional profile depending on the stage and severity of the disease, demonstrating the existence of an active mechanism of silencing their functional activity governed by the overexpression of certain inhibitory receptors.

A platform for high efficiency screening has been implemented for the discovery of new antiparasitics. A screening is being performed of more than 1000,000 natural product extracts for the discovery of new agents against malaria, leishmaniasis, Chagas disease and sleeping sickness.



CELL THERAPY NETWORK (TERCEL) – RD12/0019

Web Address: [http:// www.red-tercel.com](http://www.red-tercel.com)

Development and participation of the first clinical trial in phase III for cell therapy with positive results: "A phase III randomized clinical trial of Cx601 (expanded allogeneic adipose-derived stem cells) for complex perianal fistulas in Chron's disease". The cellular product has been developed in Spain and has a Spanish patent.

Also note the following published articles in relation to basic science and clinical trials respectively:

Ruiz-Villalba A, Simón AM, Pogontke C, Castillo MI, Abizanda G, Pelacho B, Sánchez-Domínguez R, Segovia JC, Prósper F, Pérez-Pomares JM. Interacting resident epicardium-derived fibroblasts and recruited bone marrow cells form myocardial infarction scar. *J Am CollCardiol*. 2015 May 19; 65(19):2057-66.doi: 10.1016/j.jacc.2015.03.520 PMID:25975467

Vega A, Martín-Ferrero MA, Del Canto F, Alberca M, García V, Munar A, Orozco L, Soler R, Fuertes JJ, Huguet M, Sánchez A, García-Sancho J. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. *Transplantation* 2015 Aug; 99(8):1681-90.doi: 10.1097/TP.0000000000000678. PMID:25822648.

AIDS NETWORK (RIS) – RD12/0017

Web Address: <http://www.retic-ris.net>

Within the Immunopathology and Vaccines Program, the cohort Elite Controllers of the RIS has been constituted, and with more than 600 patients complements the Long Term non-progressors cohort. The first two articles describing the cohort have been published in first decile journals, and the publication of articles on genomics from both cohorts are in the process of being published.

The Bio bank has launched the virus repository and envelope, a high value scientific material that will be offered to RIS researchers as well as external.

Worth noting in the field of vaccines, is the participation of the network groups in all the European consortia for the H2020 vaccine program, with a coordinating role of some work packages.

The RIS has developed 65 clinical trials of non-commercial interest, with more than 11,000 patients enrolled and more than 40 publications in first quartile journals derived from these studies

The cohort of patients infected by the HIV virus (CoRIS), that has recruited over 10,000 patients with samples in the Bio Bank, collaborates with CASCADE, HIV-CAUSAL, EuroCoord and ART-Collaboration and has updated its databases of ENOS Satellites, hepatitis and resistors. The database is currently being updated in order to incorporate new patients. CoRIS publishes an annual average of 5 articles.

PREVENTIVE ACTIVITIES AND HEALTH PROMOTION IN PRIMARY CARE NETWORK (REDIAPP) – RD12/0005

Web Address: www.rediapp.org

Along with strengthening activities initiated in previous years, this years highlights include the implementation and monitoring of 3 population cohorts focused on the study of fragility and the participation and coordination of several European Projects under the 7th Framework Program, DG-SANTE, H2020, IMI, KIC and Erasmus+. It is worth noting that during the last annuity the following activities have been initiated:

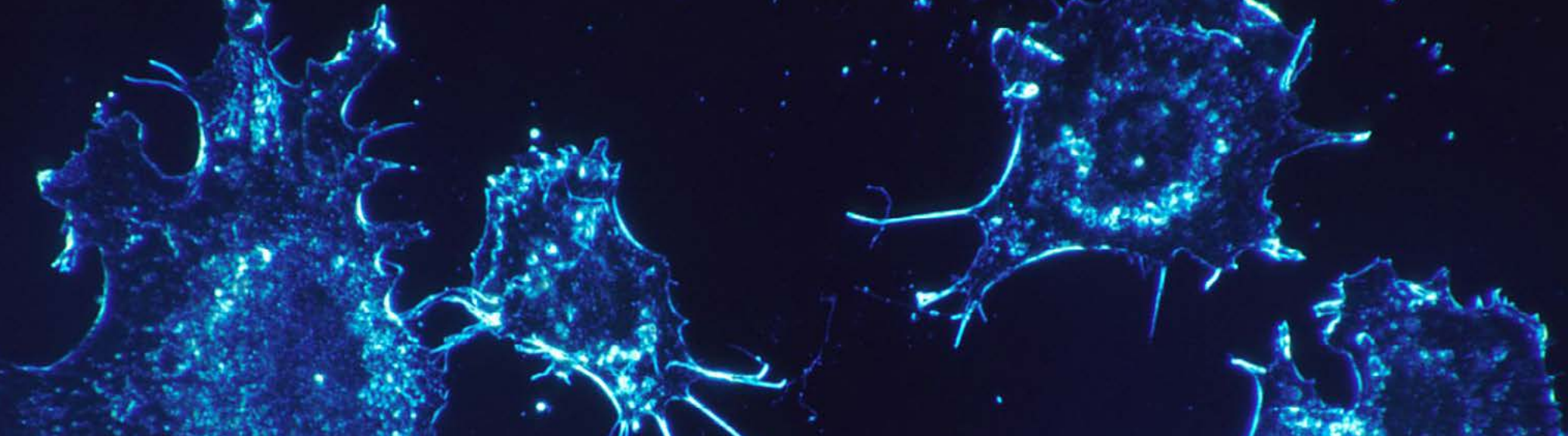
Incorporation of a new cohort (EXERNET) focused on the study of the effect of physical activity on functional status during the aging process.

Data collection performed by the third wave of the Toledo Study on Healthy Aging, which will allow the assessment, together with the predicting baseline study variables, of the impact of new variables (physical activity, body composition, arterial stiffness, adherence to Mediterranean diet, mainly) that were measured three years ago by the second wave, on the disablement process and the rest variable results.

Coordination and participation of the Joint Action of Frailty, which will begin this year and that brings 23 State Members of the European Union (UE) together in order to adopt a comprehensive framework for the entire EU and its member countries of fragility approach, indicating objectives, starting points and paths to follow.

Publication of more than a hundred collaborative papers in journals in the field of Medicine (Lancet, JCEM, Lancet Diabetes and Endocrinol), Geriatrics (JAGS, J Gerontol; JAMDA, Maturitas, Exp Gerontol, Age Aging), Gerontology (Aging Cell, Gerontology) Biologia (J Physiol, FRBM, J Pin Res.) and obtention of projects in national summons.

Participation in expert groups on a European National (EIP-AHA) and International (OMS) level, for the drafting of documents, including notably the “World Report on Ageing and Health” of the WHO (OMS in Spanish), presented on October 1, 2015, and available in several languages including Spanish.



FRAGILITY AND AGING NETWORK (RETICEF) – RD12/0043

Web Address: <http://www.reticef.es/>

Along with strengthening activities initiated in previous years, this years highlights include the implementation and monitoring of 3 population cohorts focused on the study of fragility and the participation and coordination of several European Projects under the 7th Framework Program, DG-SANTE, H2020, IMI, KIC and Erasmus+. It is worth noting that during the last annuity the following activities have been initiated:

Incorporation of a new cohort (EXERNET) focused on the study of the effect of physical activity on functional status during the aging process.

Data collection performed by the third wave of the Toledo Study on Healthy Aging, which will allow the assessment, together with the predicting baseline study variables, of the impact of new variables (physical activity, body composition, arterial stiffness, adherence to Mediterranean diet, mainly) that were measured three years ago by the second wave, on the disablement process and the rest variable results.

Coordination and participation of the Joint Action of Frailty, which will begin this year and that brings 23 State Members of the European Union (UE) together in order to adopt a comprehensive framework for the entire EU and its member countries of fragility approach, indicating objectives, starting points and paths to follow.

Publication of more than a hundred collaborative papers in journals in the field of Medicine (Lancet, JCEM, Lancet Diabetes and Endocrinol), Geriatrics (JAGS, J Gerontol; JAMDA, Maturitas, Exp Gerontol, Age Aging), Gerontology (Aging

Cell, Gerontology) Biologia (J Physiol, FRBM, J Pin Res.) and obtention of projects in national summons.

Participation in expert groups on a European National (EIP-AHA) and International (OMS) level, for the drafting of documents, including notably the “World Report on Ageing and Health” of the WHO (OMS in Spanish), presented on October 1, 2015, and available in several languages including Spanish.



CARDIOVASCULAR DISEASE NETWORK (RIC) – RD12/0042

Web Address: <http://www.redcardiovascular.com>

In the last year, the RIC has consolidated cooperative activity in its 7 programs. Worth noting because of the magnitude of collaborative efforts and scientific impact, is the collaboration in regenerative cardiology and myocardial protection. Also notable is the basic-clinical collaborations in the study of valvular disease and other structural abnormalities of the heart, and the characterization studies of the substrate of sudden cardiac death.

The development of multicenter studies on heart failure, hypertension and coronary syndromes has helped to better understand the impact of these problems in our surroundings and has resulted in relevant publications.

The creation of the Jordi Soler Soler, post-doctoral and post-MIR contracts for Young researchers, by funds coordination, has had a high dynamic impact on the Network and has served as an example for other reticular biomedical research structures.



2.4 Support Platforms for Health Sciences and Technology Research



BIOMOLECULAR AND BIOINFORMATIC RESOURCE PLATFORMS (PRB2) - PT13/0001

Web Address: <http://www.prb2.org/es/proteored>

The Platform Network of Biomolecular and Bioinformatic Resources (PRB2) was created with the primary objective of providing a high level of technologic support for the scientific community and first and foremost, for the National Health System (NHS, SNS in Spanish). All of the work programs accredit an excellent service demand.

Achieving this goal has benefited from disseminating actions (improvement and increased website content, edition of a diptych and dissemination material, etc.). Also worth noting is the celebration of the workshop held at the International University Menendez Pelayo, which was entitled “Molecular and IT tools in biomedical research” and the celebration of the “VI Scientific Meeting on Clinical Proteomics.”

Regarding research projects, all work programs participate in national and international initiatives. The result of this activity is the publication of more than 300 scientific articles.

As a final note, during this annuity, interaction with the business sector has intensified.



CLINICAL RESEARCH AND CLINICAL TRIAL UNIT PLATFORMS (SCREN) –PT13/0002

Web Address: <http://www.SCReN.es>
(en construcción)

The platform has settled its bases on the existing infrastructure (material and human resources) needed to cope efficiently to work as a network in an atmosphere of utmost professionalism. To that end, the following has been performed successfully:

The implementation of the key Technologic Architecture for the exchange of information between all members of the: Pharmacovigilance Information System, Clinical Trial Management System (CTMS) and Intranet SCReN.

The development and implementation of a quality management system, which has so far approved 17 Standard Operating Procedures that allow, harmonized networking.

The development and implementation of an internal and external training plan to equip all Platform members with the necessary skills for conducting clinical trials.

An update of operational plans for each of the four programs aimed at the overall achievement of objectives.

The accession of the SCReN Platform to the European Clinical Research Infrastructure Network (ECRIN) conveyed through the National Hub.

Internal and external dissemination of the Platform activities focused on enhancing the uptake of projects and collaborations with other agencies.

The incorporation of viable, quality projects with high impact on the NHS, so far counting with a total of 44 multicenter clinical trials that have received support from the Platform for:

The Global Management of each Project (44 clinical trials).

The completion of the Regulatory Formalities that are necessary for implementing and monitoring (44 clinical trials).

Monitoring a total of 439 recruiting centers by Platform staff.

The completion of Pharmacovigilance tasks of 26 clinical trials.

Data Management and Statistics of 6 clinical trials.

Beneficiaries: SCReN offers a solid alternative to researchers, for both national and international studies that require full or partial project support and acting upon health services and regulatory bodies in both Spain and Europe. This is thanks to its Spanish infrastructure and pan-European integration in ECRIN.



INNOVATION PLATFORM IN MEDICAL AND HEALTH TECHNOLOGIES (ITEMAS) - PT13/0006

Dirección web: <http://www.itemas.org/>

Important innovative activity reflected in the following figures: 900 captured idea, 500 innovation project under development phase, 350 in transfer and 200 that have reached the market.

Incorporation of new collaborating entities, currently a sum of about 115 entities. It is worth noting the incorporation of the first 2 international entities from Colombia.

The launch of a technology watch bulletin in collaboration with the OEPM on medical devices and the establishment of an agreement with this office for bettering the economic condition in hiring services to members and collaborators of the ITEMAS.

Completion of a scoreboard indicator with an implemented manual for measuring the variables that are involved in the activity of ITEMAS members.

Significant progress in developing a guide for good practices in innovation and document management that will serve as a basis for the implementation of the R+D+I management system and certification according to the UNE 166.002:2014 norm.



BIOBANKS PLATFORM - PT13/0010

Dirección web: <http://www.redbiobancos.es>

The National Bio bank Platform Network project brings together 42 centers throughout Spain and more than 600 agents (coordinators, technical personnel, researchers).

A total of 174 new collections that compromise 166,608 samples have been incorporated.

A total of 1,344 applications have been addressed and 135,209 bio resources have been distributed.

The bio banks participate in 35 projects/international consortia.

Implementation of the Management System Platform (IdiNet), a tool that allows us to carry out more efficient planning and monitoring.

We have held the Sixth National Bio bank Congress with the collaboration of SEOM, SEAP, GEICAM, AECC, GEPAC, EUPATI, Lleida Official College of Doctors, National Clinical Trials Platform, College of Nursing of Lleida.

2.5 Health Research Institutes (IIS)

During 2015, the Institute of Health Carlos III instructed the accreditation of seven new Health Research Institutes (IIS). They are the following:

- IIS BIOCRUCES (Biocruces Health Research Institute)
- IBIMA (Institute for Biomedical Research in Malaga)
- IMIB (Murciano Biosanitary Research Institute Virgen de la Arrixaca)

- IDIVAL (Research Institute Marqués de Valdecilla)
- INIBIC (Biomedical Research Institute A Coruña)
- IIS Aragón (Aragon Institute of Health Research)
- ibs.GRANADA (Biosanitary Research Institute Granada)

By the end of the year, 29 accredited Institutes of Health Research exist, of 10 CCAA.

In addition, during 2015 the idis (IIS de Santiago de Compostela), IdiPAZ (IIS Hospital La Paz), and the iisFJD (IIS Fundación Jiménez Díaz) renewed their accreditation.

The Accreditation Unit and the Technical Commission of Accreditation continued to attend requests for requirement information, conditions and process of accreditation of NHS hospitals that consider the possibility of creating an IIS. Prior visits to two Candidate Institutes before their formal request for accreditation were also made.

Moreover, the unit analyzed and reported on the validity of accreditation in those institutes that have undergone significant changes in their structure.





2.6 Foundations

The Institute of Health Carlos III takes part in the planning, coordination, and monitoring and scientific evaluation of the following Foundations.



CARDIOVASCULAR RESEARCH CENTER NETWORK CARLOS III

<http://www.cnic.es>

The Spanish National Cardiovascular Research Center Foundation (CNIC in Spanish) is a public-private initiative of the Institute of Health Carlos III and the Pro-CNIC Foundation that relies under the Ministry of Economy and Competitiveness, and whose aim is to promote cardiovascular health of people through

basic research, translational medicine and training, thus contributing to the progress of scientific knowledge in the field of cardiovascular health and transfer of this knowledge intended towards prevention, diagnosis and treatment of cardiovascular disease.

In 2015 the CNIC reviewed its accreditation as the Severo Ochoa Center for Excellence for the 2016-2019 period.

Scientific Production

During 2015, the CNIC published 215 articles, 195 with impact index. During this year, the CNIC has continued its international collaborations, in a way that 62% of articles were studies conducted in collaboration with foreign institutes, 29% of them with Spanish institutes and 9% of them performed solely by CNIC researchers. 60% of the total publications had a CNIC scientist as lead author.

Fundraising

From 2007 to 2015, the CNIC has achieved more than 51 M€ from national competitive funds, the majority of public origin. In 2015 researchers at the CNIC have participated in over 30 national summons and have achieved 48 successful proposals

In regard to international competitive funds, the CNIC has achieved more than 31 M€. It is also worth noting that the CNIC has been the third entity raising funds towards the PEOPLE (Marie Curie) program of the Seventh Framework Program (FP7, 7PM in Spanish) on a national level, and is the institution that has achieved the largest European funding under the new Horizon 2020 program within the Social Health, Demographic Change and Wellbeing challenge in the 2014 summon in comparison with other Spanish institutions.

The center has participated in 34 projects that were funded by the European commission in the FP7, and is involved in 10 projects under the new H2020 Program.

CNIC international excellence is reflected through the high participation and success rates of research groups in the projects denominated as European Research Council (ERC), with 5 ERC in FP7 and 4 within the H2020 program.

Patents

The CNIC is very active in the field of transferring research results and the current technological offer consists of 20 patent families. In 2015 a total of 20 patent applications were filed, taking into account extensions and new applications. Applications have been made in both the Spanish Patent and Trademark Office (SPTO) as well as in other international patent offices (EPO, USPTO, JPO). Four of the active patent families have been licensed to companies for their development and commercialization. Moreover, the CNIC generates results of interest to the biotechnology/pharmaceutical private sector, which has allowed 4 scientific collaboration agreements to be signed in 2015 for joint projects with various companies.

Training

The center's training activities are coordinated through the Global Training Plan, denominated CNIC-JOVEN, designed to bring biomedical research to the youth and create a pool of future researchers of excellence in the cardiovascular area.

In 2015, the CNIC had 669 participants throughout the different programs and training sessions. At pre-graduate level (Approach Program), at degree level (Cicerone Program), at post graduate level (Master Program, Pre-doctoral; Pre-doctoral "La Caixa", Severo Ochoa, Postgraduate Program). On a post-doctoral level, 5 researchers were hired in the European Union Cofound Program "CNIC International Postdoctoral Program". 10 doctoral theses were defended.

The training offer was completed with a Continued Education Program, in which the Cicerone Day Course for Cardiovascular Pathophysiology and Vascular Biology course were organized.

NATIONAL FOUNDATION CENTER FOR CANCER RESEARCH

During 2015 two new Junior Groups have been added to the Molecular Oncology Program: the Micro environmental and Metastasis group, and the Cerebral Metastasis group. Two new Technical Units: Protein Crystallography and Electron Microscopy.

In 2015 the CNIO renewed accreditation of the Severo Ochoa Center of Excellence for the 2016-2019 period. The accreditation meets the highest score awarded by the evaluators, who have welcomed and positively valued the research in the Center and its strategic plan 2016-2019.

The initiative that launched at the end of 2014 "Friends of the CNIO" has been consolidated, which is a philanthropic crowd funding platform that has led to reaching 560 donors by the end of the year.

Scientific Production

During 2015, the CNIO has published a total of 278 articles, 49 of which were published in journals with impact factors between 10 and 15, and 21 in journals with an impact factor greater than 15. It is worth noting that this level of excellence in scientific production has grown continuously since 2010.

Most relevant publications in 2015:

Maraver A, Fernández-Marcos PJ, Cash TP, Mendez-Petruz M, Dueñas M, Maietta P et al. NOTCH pathway inactivation promotes bladder cancer progression. *J Clin Invest.* 2015 Feb;125(2):824-30. DOI:10.1172/JCI78185. PMID:25574842.

Apellániz-Ruiz M, Lee MY, Sánchez-Barroso L, Gutiérrez-Gutiérrez G, Calvo I, García-Estévez L et al. Whole-exome sequencing reveals defective CYP3A4 variants predictive of paclitaxel dose-limiting neuropathy. *Clin Cancer Res.* 2015 Jan 15;21(2):322-8. doi:10.1158/1078-0432.CCR-14-1758. PMID: 25398452.

Wurm S, Zhang J, Guinea-Viniegra J, García F, Muñoz J, Bakiri L, Ezhkova E, Wagner EF. Terminal epidermal differentiation is regulated by the interaction of Fra7 2/AP71 with Ezh2 and ERK1/2. *Genes Dev.* 2015 Jan 15;29(2):144-56. doi:10.1101/gad.249748.114. PMID: 25547114.

Trakala M, Rodríguez-Acebes S, Maroto M, Symonds CE, Santamaría D, Ortega S et al. Functional reprogramming of polyploidization in megakaryocytes. *Dev Cell*. 2015 Jan 26;32(2):155-67. doi:10.1016/j.devcel.2014.12.015. PMID: 25625205.

Ortega-Molina A, Lopez-Guadamillas E, Mattison JA, Mitchell SJ, Muñoz-Martin M, Iglesias G et al. Pharmacological inhibition of PI3K reduces adiposity and metabolic syndrome in obese mice and rhesus monkeys. *Cell Metab*. 2015 Apr 7;21(4):558-70. doi: 10.1016/j.cmet.2015.02.017. PMID:25817535.

Lopez-Contreras AJ, Specks J, Barlow JH, Ambrogio C, Desler C, Vikingsson S et al. Increased Rrm2 gene dosage reduces fragile site breakage and prolongs survival of ATR mutant mice. *Genes Dev*. 2015 Apr 1;29(7):690-5. doi:10.1101/gad.256958.114. PMID: 25838540.

Fawal MA, Brandt M, Djouder N. MCRS1 binds and couples Rheb to amino acid-dependent mTORC1 activation. *Dev Cell*. 2015 Apr 6;33(1):67-81. doi: 10.1016/j.devcel.2015.02.010. PMID: 25816988.

Garrido-Laguna I, Hidalgo M. Pancreatic cancer: from state-of-the-art treatments to promising novel therapies. *Nat Rev Clin Oncol*. 2015 Jun;12(6):319-34. doi: 10.1038/nrclinonc.2015.53. PMID: 25824606.

García-Beccaria M, Martínez P, Méndez-Pertuz M, Martínez S, Blanco-Aparicio C, Cañamero M et al. Therapeutic inhibition of TRF1 impairs the growth of p53-deficient K-RasG12V-induced lung cancer by induction of telomeric DNA damage. *EMBO Mol Med*. 2015 May 13; 7(7):930-49 doi: 10.15252/emmm.201404497. PMID:25971796

Povedano JM, Martínez P, Flores JM, Mulero F, Blasco MA. Mice with pulmonary fibrosis driven by telomere dysfunction. *Cell Rep*. 2015 Jul 14;12(2):286-99. doi:10.1016/j.celrep.2015.06.028. PMID: 26146081.

Martínez P, Blasco MA. Replicating through telomeres: a means to an end. *Trends Biochem Sci*. 2015 Sep;40(9):504-15. doi: 10.1016/j.tibs.2015.06.003. PMID:26188776.

Ruiz S, Lopez-Contreras AJ, Gabut M, Marion RM, Gutierrez-Martinez P, Bua S, et al. Limiting replication stress during somatic cell reprogramming reduces genomic instability in induced pluripotent stem cells. *Nat Commun*. 2015 Aug 21;6:8036. doi:10.1038/ncomms9036. PMID: 26292731

Doménech E, Maestre C, Esteban-Martínez L, Partida D, Pascual R, Fernández-Miranda G et al. AMPK and PFKFB3 mediate glycolysis and survival in response to mitophagy during mitotic arrest. *Nat Cell Biol*. 2015 Oct;17(10):1304-16. doi:10.1038/ncb3231. PMID: 26322680

Calvete O, Martínez P, García-Pavía P, Benítez-Buelga C, Paumard-Hernández B, Fernández V et al. A mutation in the POT1 gene is responsible for cardiac angiosarcoma in TP53-negative Li-Fraumeni-like families. *Nat Commun*. 2015 Sep 25;6:8383. doi:10.1038/ncomms9383. PMID: 26403419.

Jacome, A, Gutiérrez-Martínez, P, Schiavoni, F, Tenaglia, E, Martínez, P, Rodríguez-Acebes S et al. NSMCE2 suppresses cancer and aging in mice independently of its SUMO ligase activity. *EMBO J*. 2015 Nov 3;34(21):2604-19. doi: 10.15252/emboj.201591829. PMID: 26443207.

Álvarez S, Díaz M, Flach J, Rodríguez-Acebes S, López-Contreras AJ, Martínez D et al. Replication stress caused by low MCM expression limits fetal erythropoiesis and hematopoietic stem cell functionality. *Nat Commun*. 2015 Oct 12;6:8548. doi:10.1038/ncomms9548. PMID: 26456157.

Morgado-Palacin L, Varetto G, Llanos S, Gómez-López G, Martínez D, Serrano M. Partial loss of Rpl11 in adult mice recapitulates Diamond-Blackfan anemia and promotes lymphomagenesis. *Cell Rep*, 2015 Oct 27;13(4):712-22. doi:10.1016/j.celrep.2015.09.038 PMID: 26489471.

Sutto L, Marsili S, Valencia A, Gervasio FL. From residue coevolution to protein conformational ensembles and functional dynamics. *Proc Natl Acad Sci USA*, 2015 Nov 3;112(44): 13567-72. doi:10.1073/pnas.1508584112. PMID: 26487681.

Hoshino A, Costa-Silva B, Shen TL, Rodrigues G, Hashimoto A, Tesic Mark M et al. Tumour exosome integrins determine organotropic metastasis. *Nature*, 2015 Nov 19;527(7578):329-35. doi:10.1038/nature15756. PMID: 26524530.

Fundraising

The CNIO finances a substantial part of its research through competitive projects of national and international institutions, as well as through private entities. In 2015, the CNIO has obtained funding of 143 projects, 31 of which were international consortia, 4 of them led from the CNIO and 35 national consortia, 8 of them coordinated by the CNIO.

International Consortiums: one project financed by AXA Research Fund; 19 projects of the European Commission; one project funded by the Massachusetts Institute of Technology (MIT); one of the Melanoma Research Alliance (MRA); three of the US NIH, one of the Paradifference Foundation, three of the US Defense Department, one of the Volkswagen Foundation and one of the WCR (formerly AICR).

Individual International Projects: Five of the International Association for Cancer Research (WCR, formerly AICR); one of the Prostate Cancer Foundation; ten of the European Commission; one of the European Foundation for the Study of Diabetes (EFSD); one of the Howard Hughes Medical Institute (HHMI); one of the Melanoma Research Alliance (MRA).

Collaborative National Projects: Nine of the Autonomous Community of Madrid; ten of the Carlos III Health Institute (ISCIII); six of the MINECO; three of the MSSSI; three of the Spanish Association Against Cancer (AECC); three of the La Marató TV3 Foundation; and one of the Madrid+d Foundation.

Individual National Projects: 15 of the ISCIII; 34 of MINECO; one of the Mutua Madrileña Foundation; two of the Ramón Areces Foundation; one of the BBVA Foundation; one of the Group of Neuroendocrine Tumors (GETNE); 1 of Spanish Society of Medical Oncology (SEOM); one of the Astrazeneca Foundation; one of the FERRO Foundation; one of the Spanish Group of Genitourinary Tumors (SOGUG); three of the Botín Foundation.

In 2015 20 contracts were negotiated with companies that ensure future revenues that are close to 10% of the CNIOs total budget. For this reason and in recognition of its work, the Innovative Enterprises Forum (FEI) granted the CNIO Innovation Program the "III Recognition of Innovation" award.

Patents

In 2015, patents have been requested for four new inventions. During 2015 the income generated by intellectual property rights has come close to 800,000€, an amount that accounts for half of all the benefits of the entire university system in Spain, placing the CNIO as a leading public institution in technologic transfer.



Training

During 2015, the CNIO has signed new agreements with universities (Polytechnic of Madrid, Castilla La Mancha, Catholic University of Murcia, Autonomous University of Barcelona, Complutense of Madrid, La Coruna, Sevilla), the Spanish Association Against Cancer, the Ministry of Education, Culture and Sports, and secondary schools (IES Moratalaz, IES Benjamín Rúa de Móstoles, IES Jaime Ferrán Clúa, IES Ramón y Cajal, Rozona Training Center and OPESA Educational Center). These agreements allow students of the mentioned institutions to conduct training practices in the CNIO.

In 2015 the Caixa Foundation awarded two students a grant for their doctoral thesis at the CNIO. In total during 2015, 15 doctoral theses have been defended. One third of the 105 pre-doctoral students who have worked in the CNIO during 2015 come from foreign universities.

The CNIO has a post doctoral training program sponsored by the Banco Santander Foundation, aimed towards attracting scientists who have developed part of their scientific career in England or the US. During 2015, a scientist originated from the Memorial Sloan Kettering Institute of Cancer Research of New York obtained this contract. In addition, the possibility of a business management and administration course through the Enterprise Institute Program is offered to bring scientists closer to the market. During 2015, the CNIO has had 48 post-doctoral students.

For medical residents, there are three continuing education programs that are developed through three-month stays in CNIO research groups. During 2015 the CNIO has had 25 resident doctors from different hospitals.

The CNIO is actively involved in postgraduate programs from diverse Spanish academic institutions, both in teaching and in offering the possibility of hosting students during their Final Masters Project.

During 2015, in the two laboratory practice programs that are studied by university students in their second cycle, 82 students have participated, 3 of who have ended up joining as pre-doctoral students.

27 Vocational Training technicians have participated in the training program organized through agreements with nine secondary schools. Five have since been hired as laboratory technicians in the CNIO.

In 2015, thanks to the Jesus Serra Foundation, the presence of the CNIO was counted on to carry out one or two month stays of 3 visiting scientist from the School of Medicine of the University of Yale; Columbia University New York; the International Institute of Molecular and Cell Biology and the University of California, Berkley.

21 speakers of international relevance have been invited within the Distinguished Seminars CNIO Program. One of the seminars was sponsored by the French Embassy and four of them by the Banco Sabadell Foundation.

During 2015 CNIO scientists organized 48 ad-hoc seminars.

In addition, the office of Women's for Science (WISE office) has organized 5 con-

ferences within the WISE seminars series. (<http://www.cnio.es/es/women-science/events.asp>). The DEAN office has also organized a series of seminars through associations and postdoctoral students.

Events

2 CNIO Frontiers Meeting o CFMs ("New Trends in Anticancer Drug Development". and "Metastasis Initiation: Mechanistic Insights and Therapeutic Opportunities"); the VI National Bio banks Congress; the III National Sarcoma Day; the I National Symposium on Applied Genomics in Oncology; the Second Meeting of the Madrid Macromolecular Structural Club; the Bioinformatics as a Driver of Innovation congress;

Role of Pharmacogenetics and Pharmacogenomics in XXI Century Medicine: Current Status and New Challenges.



FOUNDATION CENTER FOR NEUROLOGICAL DISEASES

On December 27, 2002, the Research Center for Neurological Diseases was established by Ministerial Council Agreement. It is a pro non-profit foundation of governmental scope and competition. It currently relies under the Ministry of Economy and Competitiveness through the Carlos III Institute of Health.

The CIEN Foundation is a prime example of public-private collaboration research in Spain. Since its establishment, it manages and coordinates the Alzheimer Unit Research Project (UIPA), created by the Queen Sofia Foundation and located in the Alzheimer Center that bears their name.

R+D Activities

The CIEN Foundation, as an ISCIII public foundation, joined the initiative of the Reina Sofia Foundation from its beginning, to create the Reina Sofia Alzheimer Foundation Complex (CAFRS), in order to constitute a reference in the research of degenerative dementias in our country. Eight years after the opening of the center, its two research projects, the PICAV and the Project Vallecas, represent the two main cohorts of institutionalized patients and cognitively healthy volunteers, respectively, in our research environment.

The strategic position of the CIEN Foundation in research of neuro-generative diseases is enhanced by its central role (scientific collaboration and management) with the Research Center for Neurodegenerative Diseases Network (CIBERNED), that has contributed to the development of a bio bank of neurological samples in the center (CIEN Tissue Bank), which forms part of the platform of the CIBERNED bio banks.

Cooperation between FCIEN and CIBERNED has been recognized by the European Union through the joint incorporation of both entities of the Network of Centers of Excellence in Research on Neurodegeneration (CoEN) within the Joint Program for Neurodegenerative diseases .

A recent initiative, which will contribute to the international projection of the Vallecas Project, in collaboration with other cohort studies conducted in other regions (CITA Foundation in San Sebastian and Paqual Maragall Foundation in Barcelona), is the joint incorporation to the European Prevention of Alzheimer's Dementia Consortium. Particularly as regards the maintenance and management of biological samples from the aforementioned CIEN Foundation projects, the CIEN Tissue Bank in the National Bio bank Platform Network, promoted by the ISCIII, has a relevant participation.

Scientific Production

In 2015, researchers at the CIEN Foundation produced 46 scientific publications, 36 of them (78.26%) in journals of their category classified in first and second quartile. During 2015, 30 original articles were published in specialized journals in first and second quartiles, with an average impact factor of 4.718, representing an increase of (8.039%) compared to 2014.

In 2015, the article that describes the objectives and methodology employed in the Vallecas Project was published in the journal *Frontiers in Aging Neuroscience*.

The most relevant publications during 2015 were:

Zea-Sevilla MA, Fernandez-Blazquez MA, Calero M, Bermejo-Velasco P, Rabano A. Combined Alzheimer and cerebrovascular staging explains advanced dementia cognition. *Alzheimers Dement*. 2015 Nov;11(11):1358-66. doi: 10.1016/j.jalz.2015.01.004. PMID: 25804997

Alcolea D, Martinez-Lage P, Sanchez-Juan P, Olazarán J, Antúnez C, Izaguirre A, et al. Amyloid precursor protein metabolism and inflammation markers in preclinical Alzheimer disease. *Neurology*. 2015 Aug;85(7):626-33. doi: 10.1212/WNL.0000000000001859. PMID: 26180139.

Strange BA, Yebra M. The multi-instrumentalist hippocampus: Comment on "The quartet theory of human emotions: An integrative and neurofunctional

model" by S. Koelsch et al. *Phys Life Rev*. 2015 Jun;13: 85-6. doi: 10.1016/j.plrev.2015.04.028. PMID: 25921634.

González-Rosa JJ, Soto-León V, Real P, Carrasco-López C, Foffani G, Strange BA, Oliviero A. Static Magnetic Field Stimulation over the Visual Cortex Increases Alpha Oscillations and Slows Visual Search in Humans. *J Neurosci*. 2015 Jun 17;35(24): 9182-93. doi: 10.1523/JNEUROSCI.4232-14.2015 PMID: 26085640

Pisa D, Alonso R, Rábano A, Rodal I, Carrasco L. Different Brain Regions are Infected with Fungi in Alzheimer's Disease. *Sci Rep*. 2015 Oct 15;5:15015. doi: 10.1038/srep15015. PMID: 26468932

Camacho FII, Cabanas-Perianes V, Coll JM, Gutierrez AR, Cuartero-Perez B, de Sampedro JR, et al. Case report: Cerebral lighth chain deposition disease (LCDD). *Haematologica*. 2015; 100(s1):747-8. Resumen n PB1898

Rieu I, Martinez-Martin P, Pereira B, De Chazeron I, Verhagen Metman L, Jahanshahi M, et al. International validation of a behavioral scale in Parkinson's disease without dementia. *Mov Disord*. 2015 Apr 15;30(5):705-13. doi: 10.1002/mds.26223. PMID: 25809278

Erro R, Picillo M, Amboni M, Moccia M, Vitale C, Longo K, et al. Nonmotor predictors for levodopa requirement in de novo patients with Parkinson's Disease. *Mov Disord*. 2015 Mar;30(3):373-8. doi: 10.1002/mds.26076. PMID: 25648938

Ruiz-Riquelme A, Sánchez-Iglesias S, Rábano A, Guillén-Navarro E, Domingo-Jiménez R, Ramos A, et al. Larger aggregates of mutant seipin in Celia's Encephalopathy, a new protein misfolding neurodegenerative disease. *Neurobiol Dis*. 2015 Nov;83:44-53. doi: 10.1016/j.nbd.2015.08.006. PMID: 26282322

Alonso R, Pisa D, Marina AI, Morato E, Rábano A, Rodal I, Carrasco L. Evidence for fungal infection in cerebrospinal fluid and brain tissue from patients with amyotrophic lateral sclerosis. *Int J Biol Sci*. 2015 Apr 2;11(5): 546-58. doi: 10.7150/ijbs.11084. PMID: 25892962.

Fundraising

The Foundation is committed to promoting youth employment and implementation of the Youth Guarantee R+D+I in the National Sub-Programme of Incorporation, of The National Programme for Talent and its Employability, under the framework of the National Plan for Scientific and Technical Research and Innovation 2013-2016, having formalized four contracts in 2015.

The agreement was formalized with the Community of Madrid in collaboration with the Massachusetts Institute of Technology (MIT) in the Project M+VISION to attract international researchers "of recognized prestige" within the program COFUND of

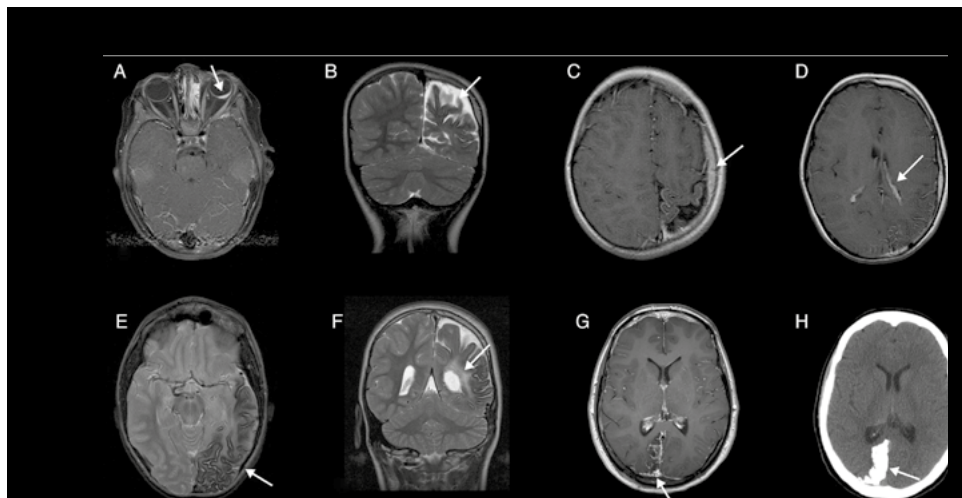
the Seventh Program Framework, within the framework of the FP7-PEOPLE-2011-COFUND summon.

In 2015, the BT-CIEN reached its donation No. 600, and also reached a record of total annual donations (76), and for each of the donation sub-programs, the external (63), and the internal (13), aimed at patients of the Alzheimer Center Fountain Reina Sofia.

The Association of Entrepreneurs of Hospitality and Tourism in Fuerteventura distinguished the CIEN Foundation as the beneficiary of the Fuerteventura Grant to contribute to the funding of research into Alzheimer's disease.

Patents

During 2015, 3 patents remain ongoing, active in national and international stages, which are currently under agreement of a co-ownership with participation of the CIEN Foundation.



Other Activities

- The Neuroimaging Department has conducted 5,547 MRI studies on 963 people.
- At the European Congress of Radiology 2015, the neuroimaging team received the Certificate of Merit for the presentation "Image acquisition protocol of olfactory system".
- In 2015, the recruitment of participants concluded in the multicentric project sponsored by the CIEN Foundation along with the Leon and Soria Alzheimer Associations for the detection of the protein TAU in tears as a potential biomarker of Alzheimer's disease. In September 2015, the third International Congress of Research and Innovation in Neurodegenerative Diseases (CIIEN) was held, which has established itself as the International Congress of reference in our country in the area of neurodegenerative diseases.
- As in previous years, on November 8, 2015, International Radiology Day was celebrated in the CIEN Foundation- Reina Sofia Foundation, which was broadcast live through streaming, leading to over 1.5 million impressions in the conversation #IdorSPAIN.
- The Vallecas Project received the INESE Award in the XV edition of the Solidarity Awards of Insurance 2015.
- The BT-CIEN renewed its accreditation of the Quality Management Program EI BT-CIEN, ISO 9001/2008, after four years of development. IT was launched in the T-CIEN Sample Management area, dedicated to the management, processing and tracking of requests for samples. The management area in the CIEN Foundation has renewed the ISO 9001:2008 certificate, as requirement standards were met in said norm. The validity of the certificate is of three years.
- In December 2015, coinciding with the holidays, the "Memory Tree" was inaugurated with the support of the District Board of Villa de Vallecas, the Major General Directorate of the Community of Madrid and the Municipal Market of Villa de Vallecas.
- In 2015, Responsive Web Design, a new website of the HUNDRED foundation was published. During 2015 around 100,000 users visited the site.
- Presence of the CIEN Foundation increased during 2015 by 23% compared to 2014, due to a 109% increase in print media presence and 13% of digital media.



3

**Scientific-Technical
Activities**

3 Scientific-Technical Activities

3.1 Centers and Units

The most relevant scientific and technical activities during 2015 in the Centers and Units that are a part of ISCIII are specified below.

NATIONAL MICROBIOLOGY CENTER

The National Microbiology Center (CNM) has the specific mission of providing scientific-technical support to the General State Administration, Autonomous Communities and the National Health System in prevention, diagnosis and treatment of infectious diseases.

The major milestones in 2015 were:

The CNM Alerts System that has functioned 24 hours 7 days a week, has intervened in the imported cases suspected of suffering diseases caused by the Ebola virus as a continuation of the task initiated in 2014.

The CNM has participated in the study of Chikungunya fever that spread in countries of the Caribbean, Central and South America, registering several hundred cases imported into Spain by travelers from that geographical area.

In December 2015 the first diagnostic requests of the Zika virus arrived, and CNM researchers have collaborated with an international consortium of researchers for the study of a meningococcal disease by serogroup W outbreak that affects a significant number of countries in the Americas, Europa and Africa. (*J Infect.* 2015 Nov; 71(5): 544-52. doi: 10.1016/j.jinf.2015.07.007).

Scientific-Technical Activities

- THE CNM maintains 25 Microbiological Surveillance programs of infections relevant to public health that are reviewed and renewed annually. The data generated by these programs have allowed control and/or prevention measures by health authorities.
- During 2015, 126 competitive funding research projects have been maintained active, 20 of which came from international agencies. The CNM participates in the 3rd Health Program with the project EMERGE Efficient response to highly dangerous and emerging pathogens at EU level, starting from 2014 until 2017.
- The CNM coordinates ViroRed, the thematic network of the Ibero-American Science and Technology for Development Program (CYTED), formed by health laboratories and university institutes from 14 American countries, Portugal and Spain.

- The CNM has received close to 100,000 diagnostic and or reference requests through its samples management program, and more than 150,000 determinations have been performed in all of the programs activities in monitoring, alerts, outbreaks, portfolio of services and institution or company contracts. In addition to these figures, the execution of more than 100,000 DNA sequences has been carried out by the CNM Genomics Unit.
- In 2015, 6 new units and 23 new trials of the service portfolio were accredited. The CNM currently has 23 units and 87 trials accredited /certified of the service portfolio.

Scientific Production

In 2015 more than 150 publications and several hundred communications in scientific congresses and meetings of different order have been produced. Various patents and utility models have also been developed. A selection of some of the published work would include:

Oteo J, Ortega A, Bartolomé R, Bou G, Conejo C, Fernández-Martínez M et al. Prospective multicenter study of carbapenemase producing Enterobacteriaceae from 83 hospitals in Spain: High in vitro susceptibility to colistin and meropenem. *Antimicrobial Agents Chemother.* 2015; 59(6):3406-12. doi: 10.1128/AAC.00086-15. PMID:25824224

Forastiero A, Garcia-Gil V, Rivero-Menendez O, Garcia-Rubio R, Monteiro MC, Alastruey-Izquierdo A, Jordan R, Agorio I, Mellado E. Rapid development of *Candida krusei* echinocandin resistance during caspofungin therapy. *Antimicrob Agents Chemother.* 2015 Nov;59(11): 6975-82. doi: 10.1128/AAC.01005-15. PMID:26324281

Gilman MS, Moin SM, Mas V, Chen M, Patel NK, Kramer K, Zhu Q, Kabeche SC, Kumar A, Palomo C, Beaumont T, Baxa U, Ulbrandt ND, Melero JA, Graham BS and McLellan JS. Characterization of a human antibody specific for the trimeric, cleaved prefusion RSV F glycoprotein. *PLoS Pathog.* 2015 Jul 10;11(7)e1005035 doi:10.1371/Journal.ppat.1005035. PMID:26161532

Jiménez-Jorge S, de Mateo S, Delgado-Sanz C, Pozo F, Casas I, Garcia-Cenoz M, Castilla J, Rodríguez C, Vega T, Quinones C, Martínez E, Vanrell JM, Giménez J, Castrillejo D, Altzibar JM, Carril F, Ramos JM, Serrano MC, Martínez A, Torner N, Pérez E, Gallardo V, Larrauri A; Spanish Influenza Sentinel Surveillance System. Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data. *Euro Surveill.* 2015 Jul 16;20(28). pii: 21187. PMID: 26212144.

Pineda-Tenor D, Berenguer J, García-Álvarez M, Guzmán-Fulgencio M, Carrero A, Aldamiz-Echevarría T, Tejerina F, Diez C, Fernández-Rodríguez A, Jiménez-Sousa MA, Muñoz-Fernández MA, Resino S. Single nucleotide polymorphisms of

CXCL9-11 chemokines are related with liver fibrosis in HIV/HCV-coinfected patients. *J AcquirImmuneDeficSyndr.* 2015Apr 1;68(4): 386-395.doi:10.1097/QAI.0000000000000491.PMID:25559603

Avellon A, Morago L, Garcia-Galera del Carmen M, Munoz M, Echevarría JM. Comparative sensitivity of commercial tests for hepatitis E genotype 3 virus antibody detection.*J Med Virol.* 2015 Nov;87(11): 1934-9.doi: 10.1002/jmv.24251. PMID:25959136

Cabrerizo M, Trallero G, Pena MJ, Cilla A, Megias G, Muñoz-Almagro C del Amo E, Roda D, Mensalvas AI, Moreno-Docón A, García-Costa J, Rabella N, Omeñaca M, Romero MP, Sanbonmatsu-Gámez S, Pérez-Ruiz M, Santos-Muñoz MJ, Calvo C, study group of "Enterovirus and parechovirus infections in children under 3 years-old, Spain". Comparison of epidemiology and clinical characteristics of infections by human parechovirus vs. those by enterovirus during the first month of life.*Eur J Pediatr.* 2015 Nov;174(11):1511–6.doi: 10.1007/s00431-015-2566-9. PMID:25982340

Puig C, Tirado-Velez JM, Calatayud L, Tubau F, Garmendia J, Ardanuy C, Marti S, de la Campa AG, and Liñares J. Molecular characterization of fluoroquinolone resistance in nontypeable *Haemophilus influenzae* clinical isolates. *Antimicrob Agents Chemother* 59: 461-466 (2015).

Abad R, Biolchi A, Moschioni M, Giuliani MM, Pizza M, Vázquez JA. A large portion of meningococcal antigen typing system-negative meningococcal strains from Spain is killed by sera from adolescents and infants immunized with 4CMenB.*Clin Vaccine Immunol.* 2015 Apr;22(4): 357-60.doi: 10.1128/CVI.00669-14. PMID:25630407

Johnstone C, Lorente E, Barriga A, Barnea E, Infantes S, Lemonnier FA, David CS, Admon A, López D. The viral transcription group determines the HLA class I cellular immune response against Human Respiratory Syncytial Virus. *Mol Cell Proteomics.* 2015 Apr;14(4): 893-904.doi: 10.1074/mcp.M114.045401. PMID:25635267.

Training

Numerous educational activities have been conducted, having received about 200 external rotators and national and international visitors during educational and training periods in 2015.

The most relevant activities in this aspect are:

– Official Master of Microbiology for Public Health and Research of Infectious Diseases coordinated with the University of Alcalá de Henares, with the participation of more than 60 CNM professors

– Master in Virology, of the University Complutense (UCM), in which 20 CNM researchers have participated through an ISCIII-UCM collaboration, teaching or coordinating subjects

NATIONAL EPIDEMIOLOGY CENTER

The mission of the National Epidemiology Center (CNE) is to analyze the public health situation in Spain and the impact of health policies on the population. The CNE is responsible for 1.) The National Epidemiological Surveillance Network (RENAVE). 2) Training epidemiologists. 3) Epidemiological research. 4) The Spanish contribution to the European Epidemiological Surveillance of the European Center for Disease Control (ECDC).

Scientific-Technical Activities

Within the scope of their medical skills, under the tutelage of the Ministry of Health Social Services and Equality, the CNE works in all activities, plans and actions for the control, prevention and/or elimination of diseases. The areas of activity focus on:

Chronic diseases and impact of health policies: 1) Environmental Epidemiology and Cancer: Monitoring the situation of cancer in Spain. Environmental epidemiology, occupational epidemiology and lifestyle, both from an ecological point of view, studying the possible effects of industrial pollution or physical agents, research related to bio monitoring in general population, as well as genetic and molecular epidemiology of cancer, especially breast cancer. 2) Applied Epidemiology: Epidemiology of cardiovascular and neurodegenerative diseases. Monitoring the impact of health policies, aging, disability and methods for evaluation. Registration of diseases caused by prions. Epidemiology of mental health. 3) Health Situation Analysis: On-line update of mortality, analysis of inequalities social determinants. Epidemiology of deaths from external causes, and disability and accident analysis.

Transmissible diseases and risk behavior: 1) Epidemiological surveillance management of the 60 Diseases of Obligatory Declaration and notification of outbreaks to the RENAVE through the notification web platform (SiViEs).

Assessing the Alert Control And Health Emergencies (CCAES) center in transmissible disease surveillance, point of contact for international organizations on issues of surveillance and transmissible diseases; Development of the daily mortality monitoring system (MOMO); Management of the monitoring systems involved in monitoring influenza activity, surveillance of diseases that are preventable by immunization through elimination and control programs. Commissioning of the surveillance system for Infections related to Health Care. Participation in the Strategic Plan for the Control of Antimicrobial Resistances. 2)

Epidemiology of HIV/AIDS/STDs and risky sexual behaviors. 3) Risk behaviors and socially vulnerable populations: monitoring alcohol and psychoactive substance consumption and evaluation control policies, collaborating with the National Drug plan and the EMCDDA; translation of harm reduction policies to Eastern European countries in collaboration with CHAFEA; evaluation of policies for early diagnosis of HIV, especially fast testing and auto tests, in collaboration with the National Aids Plan; driving policy and social inequality assessment.

Research Projects: 52 national; 16 international

Scientific Production

In 2015 23 national publications and 123 international publications have been produced, the most prominent are:

Belza MJ, Hoyos J, Fernández-Balbuena S, Diaz A, Bravo MJ, de la Fuente L; Madrid HIV rapidtestinggroup. Assessment of an outreach street-based HIV rapid testing programme as a strategy to promote early diagnosis: a comparison with two surveillance systems in Spain, 2008–2011. *Euro Surveill.* 2015Apr 9; 20(14): pii=21089. PMID: 25884149.

de Pedro-Cuesta J, Rábano A, martinez-Martin P, Ruiz-Tovar M, Alcalde-Cabero E, Almazán-Isla J et al. Comparative incidence of conformational, neurodegenerative disorders. *PLoS One* 2015 Sep 3; 10 (9): e0137342. doi:10.1371/journal.pone.0137342. PMID:26335347

Diaz A, del Romero J, Rodriguez C, Alastrue I, Belda J, Bru FJ et al. Effects of region of birth, educational level and age on late presentation among men who have sex with men newly diagnosed with HIV in a network of STI/HIV counselling and testing clinics in Spain. *Euro Surveill* 2015Apr 9;20(14):pii=21088. PMID:25884148.

García-Pérez J, López-Abente G, Gómez-Barroso D, Morales-Piga A, Romaguera EP, Tamayo I et al. Childhood leukemia and residential proximity to industrial and urban sites. *Environ Res.* 2015 Jul;140:542-53. doi:10.1016/j.envres.2015.05.014. PMID: 26025512.

Garrido-Esteba M, Nuñez OG, León-Gomez I, Cano R, Herruzo R. Meningococcal C conjugate age-dependant long-term loss of effectiveness. *Vaccine.* 2015May 5;33(19):2221-7. doi: 10.1016/j.vaccine.2015.03.044. PMID:25819711

Culqui DR, Rodriguez-Valin E, Martínez de Aragón MV. Epidemiology of hospitalization for tuberculosis in Spain: Analysis of of the minimum basic set of data1999-2009. *EnfermInfeccMicrobiolClin.* 2015 Jan,33(1):9-15 doi: 10.1016/j.eimc.2013.12.015. PMID:24679447.

Hernando V, Álvarez-del Arco D, Alejos B, Monge S, Amato-Gauci AJ, Noori T et al. HIV infection in migrant populations in the European Union and European Economic Area in 2007-2012: an epidemic on the move. *J AcquirImmuneDefic Syndr.* 2015 Oct 1;70(2):204-11. doi: 10.1097/QAI.0000000000000717. PMID:26068723

Herrador Z, Perez-Formigo J, Sordo L, Gadisa E, Moreno J, Benito A et al. Low Dietary Diversity and Intake of Animal Source Foods among School Aged Children in LiboKemkem and Fogera Districts, Ethiopia. *PLoS.One.* 2015 Jul 23,10(7):e0133435. doi: 10.1371/journal.pone.0133435. PMID:26203904

Jiménez-Jorge S, de Mateo S, Delgado-Sanz C, Pozo F, Casas I, García-Cenoz M et al; Spanish Influenza Sentinel Surveillance System. Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data. *Euro Surveill.* 2015 Jul 16;20(28). pii=21187. doi:10.2807/1560-7917.ES2015.20.28.21187PMID:26212144

Masa Calles J. Measels. The challenges in the last phase of the removal process in Spain and Europe. *Emerging diseases* , 2015;14:25-27

Training

Applied Epidemiology Field Program (PEAC): Led by the CNE since 1994. During 2015, 11 epidemiologists were trained, participating in 32 epidemiological studies. Internationally, the OEAC participates in the Global Network of Training Programs for Epidemiologists for Public Health Intervention (TEPHINET) and collaborates with GOARN in a mission response to the Ebola virus epidemic in Africa. The 2nd year of the European project MEDIPIERT, led by the Spanish consortium ISCII-FIAP , has been consumated,

The CNE has participated in 105 seminars; 90 teaching programs; rotated 11 MIR, directed 20 Doctoral Theses and participated in 15 Courts of Theses.

NATIONAL CENTRE FOR ENVIRONMENTAL HEALTH

The mission of the National Center for Environmental Health (CNSA) is to protect the health of the Spanish population, identifying health problems arising from environmental pollution. CNSA laboratories operate under a system of quality and are accredited according to the UNE-EN ISO/IEC 17025 Norm by the National Accreditation Entity (ENAC) for 154 trials.

Scientific-Technical Services:

136,179 trials, 170 bioassays and 26 calibrations of ozone transfer standards versus national standards were performed. Development of 67 reports for the European Authority as experts in risks assessment of active substances and phytosanitary products.

Design of the quality assurance program and elaboration of the SOP, under the UNEP/WHO Project "Development of a Plan for Global Monitoring of Human Exposure to Environmental Concentrations of Mercury".

Collaboration with the office of WHO Europe as quality experts in human bio monitoring and participation in the WHO Ministerial Conference of the OMS on the European Environmental and Health process in Haifa (Israel).

The National Reference Laboratory for Air Quality (R.D.102/2011) organized two inter-comparison exercises with the participation of 16 air quality networks of regional governments and local authorities, "in situ" of dioxide nitrogen monoxide and nitrogen dioxide and the elaboration of 4 national documents.

As stakeholder of the National Ozone Standard, organization of an inter-comparison exercise of calibration of analyzers with 5 accredited laboratories.

Participation in the National Management Council Platform for R+D on Radiological Protection (PEPRI) and the COST EMF-MED" action group, network of European cooperation in research and technology on the beneficial biological effects of electromagnetic fields.

Assessment of air quality by polycyclic aromatic hydrocarbons, following an environmental incident in Castilla and Leon. Monitoring of 3 surveillance networks and 1 testing laboratory in compliance with the Directive 2015/1480/CE.

Scientific-technical and advisory support in the Command Post of Operations under the Daimiel 2015 emergency exercise organized by the Military Emergency Unit of the Ministry of Defense.

Fundraising:

Management entrustment remains active with the INIA and the MSSIS (Risk evaluation of phytosanitary products on human health) and AEMET (Air quality), and more than 400 collaborative agreements have been maintained with various entities, both public and private, for dosimetric control. The projects (FIS-ISCI) on electromagnetic fields, DGUI Community of Madrid on drug residues in water and IB-BIOALERNET, as well as a European pre-normative research project on air quality remain in effect. 11 new air quality collaboration contracts have been signed as well as the European Project BRIDGE-Health (EC 3rd Health Program). 3 new management commissions with MAGRAMA have been accepted. One for improving the quality of data, one for the calibration of transfer standards versus national ozone standards and a third for monitoring persistent organic pollutants in humans.

Scientific Production

A total of 23 scientific articles have been published (first quartile), including:

Castaño A, Cutanda F, Esteban M, Part P, Navarro C, Gómez S et al. Fish consumption patterns and hair mercury levels in children and their mothers in 17 EU countries. *Environ Res.* 2015 Aug;141:58-68. doi:10.1016/j.envres.2014.10.029.PMID:25667172

García-Camero JP, García-Cortés H, Valcárcel Y, catalá M. Environmental concentrations of the cocaine metabolite benzoylecgonine induced sublethal toxicity in the development of plants but not in a zebrafish embryo-larval model. *J Hazard Mater.* 2015 Dec 30;300:866–872. doi: 10.1016/j.jhazmat.2015.08.019. PMID:26340554

Escudero M, Viana M, Querol X, Alastruey A, Díez Hernández P, García Dos Santos S, Anzano J. Industrial sources of primary and secondary organic aerosols in two urban environments in Spain. *Environ Sci Pollut Res Int.* doi:10.107/s11356-015-4228-x.PMID:25721527

López-Herranz A, Cutanda F, Esteban M, Pollán M, Calvo E, Pérez-Gómez B et al; Bioambient.es. Cadmium levels in a representative sample of the Spanish adult population: the Bioambient.es project. *J Expo Sci Environ Epidemiol.* 2015 Apr 22. doi:10.1038/jes.2015.25.PMID:25899448

Outstanding performances at conferences

Closing Conference of the XIII Congress of Environmental Health and Invited Conference of the IX National Conference on Endocrine Disruptors. (Cartagena, 24-26 June).

Participation of the Standardization committee and Institutional representation.

Chairman of the Technical Committee of Standardization AEN/CTN 77 "environment", Chairman and Speaker of the Subcommittee AEN/CTN 77/sc 2 "air", speaker of the subcommittee AEN/CTN 77/sc1 "water" and Speaker of the AEN/CTN 215 "electromagnetic fields"

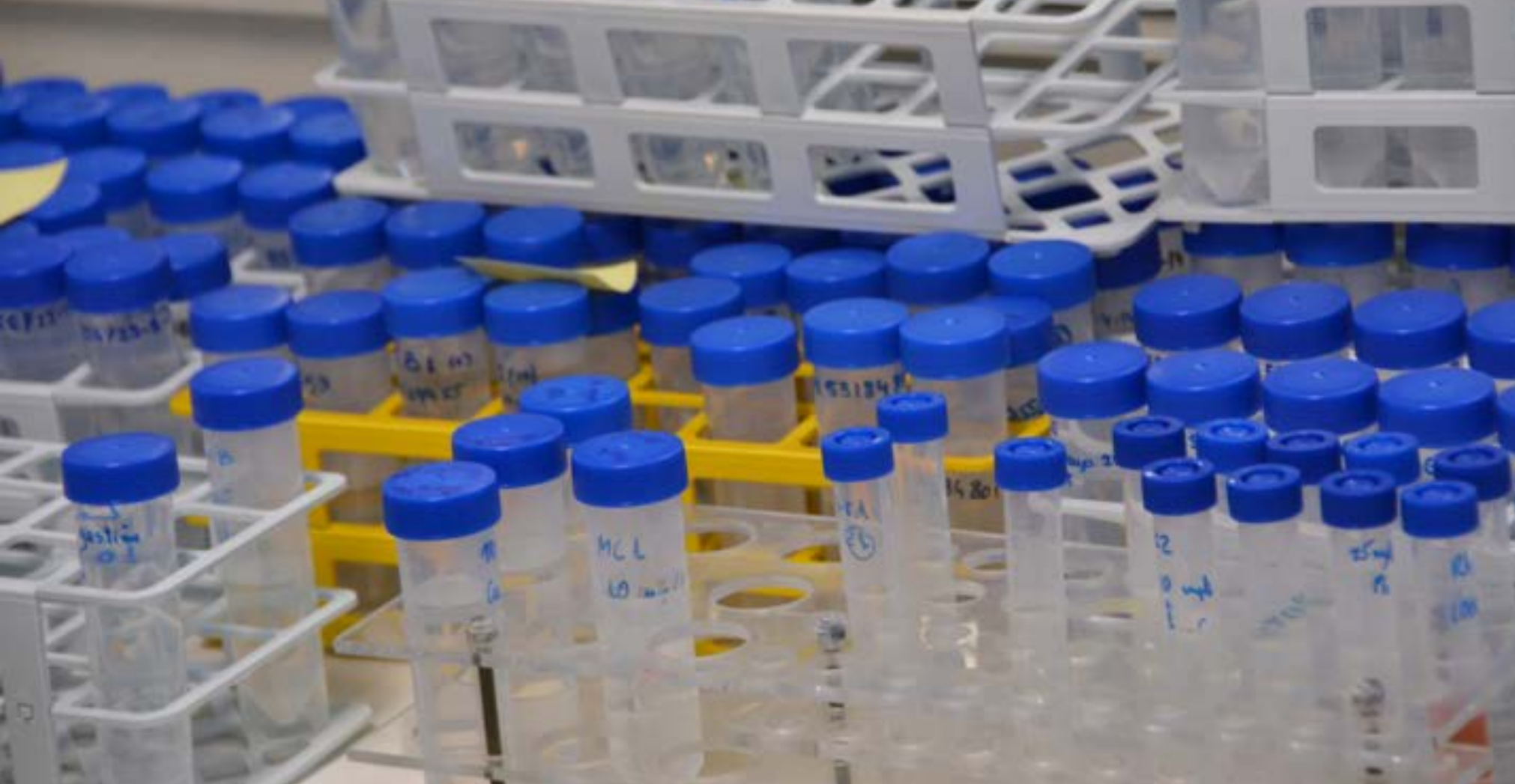
Participation in WG 34 and 21 of CEN/TC 264 "air quality".

Members of the Steering Group of the European Initiative for Human Bio monitoring (EHBMI) Research D.G. (C.E.)

Speaker of the Commission for Quality and Treatment of the Spanish Association of Water Supply and Sanitation. AEAS of the III Working Group: Water Quality of the Climate Change and Health Observatory.

Training

Imparting and organizing internal and external seminars, teaching at 16 courses (9 Masters) organized by various Spanish universities and the ENS. Coordination of the atmospheric pollution module in the URJC Environmental Pollution Master.



Impartation and organization of internal and external seminars, teaching of 16 courses (9 Masters) organized by various Spanish University and the ENS. Organization and impartation of the online course on indoor air quality in collaboration with the ENMT.

The direction of M.Bartolomé's Doctoral Theses has been carried out. UNED (cum laudem), and the Co-Direction of end-of-degree projects (TFG) and the Tutoring of external practices in collaboration with University Alfonso X. TESA Practices.

Training of Master students with the Autonomous University of Madrid ("Inland Water Quality Assessment Master")

NATIONAL CENTER OF TROPICAL MEDICINE

The National Center of Tropical Medicine was created by order of December 27, 2001 (published in the Official National Gazette (BOE) of January 11, 2002) to respond to the increasing international mobility (immigration and travelers) and also because of the increased Spanish presence in international coopera-

tion programs, with the aim of strengthening assistance, research and teaching functions in tropical diseases and to establish scientific and technical programs with countries where these pathologies exist.

Scientific-Technical Activities

- Contract with the Ministry of Health and Social Welfare Program of Equatorial Guinea and the African Development Bank for conducting Technical Assistance for the development of the National Laboratory of Public Health of Equatorial Guinea.
- RETIC Coordination "Collaborative Tropical Disease Research Network (RICET) and coordination of the research program "Program for prevention and control of high impact imported and re-emerging tropical diseases"
- Agreement with the Spanish Foundation for International Cooperation, Health and Social Policy (FCSAI) of the Ministry of Health, Social Services and Equality (MSSSI) for the implementation of the "Extension of the Pilot Project to implement continuous improvement plans for management and control of Malaria, HIV/AIDS and Tuberculosis at hospital levels in the coastal provinces of Kie Ntem and Wele Nzás, Equatorial Guinea" funded by AECID.



- Agreement with the Action Against Hunger Foundation for the realization of the Diploma “Nutrition and food security in the context of international cooperation: from diagnosis to action” during 2016.
- “Anti-malarial resistance mutations: differences in areas with different endemicity in Equatorial Guinea and Ethiopia” Project.
- Accessibility and Use of Health Services for the Diagnosis of Chagas Disease in the Community of Madrid Project.
- “Functional characterization of MBL (Mannose Binding Lectin) of *Trypanosoma brucei gambiense* implicated in human serum: new therapeutic and diagnostic target” Project.

Training

Doctoral Thesis: Nutritional status and diet of school age children in the region of Amhara (Ethiopia). Zaida Herrador Ortiz. Complutense University of Madrid. School of Medicine.

Scientific Production

Ncogo P, herrador Z, Romay-Barja M, García-Carrasco E, Nseng G, berzosa P et al. Malaria prevalence in Bata district, Equatorial Guinea: a cross-sectional study. *Malar J*. 2015 Nov 16;14(1):456. doi: 10.1186/s12936-015-0986-7. PMID:26573911.

Romay-Barja M, Jarrin I, Ncogo P, Nseng G, Sagrado MJ, Santana-Morales MA et al. Rural-Urban Differences in Household Treatment-Seeking Behaviour for Suspected Malaria in Children at Bata District, Equatorial Guinea. *PLoSOne*. 2015 Aug 18;10(8):e0135887. doi: 10.1371/journal.pone.0135887. PMID:26284683

Cordon-Obras C, Rodriguez YF, Fernandez-Martinez A, Cano J, Ndong-Mabale N, Ncogo-Ada P et al. Molecular evidence of a *Trypanosoma brucei gambiense* sylvatic cycle in the human African trypanosomiasis foci of Equatorial Guinea. *Front Microbiol*. 2015 Jul 24;6:765. doi: 10.3389/fmicb.2015.00765. PMID: 26257727.

Herrador Z, Perez-Formigo J, Sordo L, Gadisa E, Moreno J, Benito A et al. Low Dietary Diversity and Intake of Animal Source Foods among School Aged Children in LiboKemkem and Fogera Districts, Ethiopia. *PLoSOne*. 2015 Jul 23,10(7):e0133435 .doi: 10.1371/journal.pone.0133435. PMID:26203904

Mekonnen D, Admassu A, Mulu W, Amor A, Benito A, gelaye W et al. Multidrug-resistant and heteroresistant *Mycobacterium tuberculosis* and associated gene mutations in Ethiopia. *Int J Infect Dis*. 2015 Oct;39:34-8. doi:10.1016/j.ijid.2015.06.013. PMID: 26119857.

Alvarez P, Martín L, Prieto L, Obiang J, Vargas A, Avedillo P et al. HIV-1 variability and viral load technique could lead to false positive HIV-1 detection and to erroneous viral quantification in infected specimens. *J Infect*. 2015 Sep;71(3):368-76. doi: 10.1016/j.jinf.2015.05.011. PMID: 26033694.

Herrador Z, Rivas E, Gherasim A, Gomez-Barroso D, Garcia J, Benito A, Aparicio P. Using hospital discharge database to characterize Chagas disease evolution in Spain: there is a need for a systematic approach towards disease detection and control. *PLoS Negl Trop Dis*. 2015 Apr 17;9(4):e0003710. doi: 10.1371/journal.pntd.0003710. PMID: 25884198.

Cuadros J, Pérez-Tanoira R, Prieto-Pérez L, Martín-Martín I, Berzosa P, González V et al. Field Evaluation of Malaria Microscopy, Rapid Malaria Tests and Loop-Mediated Isothermal Amplification in a Rural Hospital in South Western Ethiopia. *PLoSOne*. 2015 Nov 10;10(11):e0142842. doi: 10.1371/journal.pone.0142842. PMID:26555068

RESEARCH INSTITUTE FOR RARE DISEASES

The functions of the Institute for Rare Diseases (IIER), are diagnosing, researching and registering rare diseases, including congenital abnormalities, autism spectrum disorders and Toxic Oil Syndrome.

Service Activity

The National Bio Bank of Rare Diseases (BioNER) continues its activity within the ISCIII Bio bank Platform and the European Eurobiobank and RDD-CONNECT networks. During 2015, 51 new donors have been quantified.

Genetic Diagnosis Services

The genetic diagnosis unit is accredited according to the ISO15189 standard issued by the ENAC, and is the only Spanish laboratory with this distinction in quality for identifying genetic alterations in retinoblastoma. Current activity development includes the diagnosis of rare childhood tumors and deficit of alpha-1 antitrypsin. It is also responsible for the genetic diagnosis of rare undiagnosed diseases program and for the BioNER. This year 4576 trials have been performed on 533 cases.

Patient consultation and organization system

661 consultations have been received, 335 of which belong to issues related to rare diseases and the rest relating to Toxic Oil Syndrome.

Lines of research into rare diseases

The IIER carries out basic and translational research in the field of rare diseases, Toxic Oil Syndrome and Autism Spectrum Disorders. The main lines of research are: 1) The role of the innate immune system alterations in rare diseases 2) Study of rare pediatric tumors: genetic alterations and cellular therapies. Study of laminopathies: gene and cell therapy 3) Implication of microRNAs in the development of rare diseases and their role as biomarkers, 4) Application of new genetic analysis technologies in the diagnosis of rare diseases, 5) Epidemiology of rare diseases, 6) Risk factors and prevention of congenital anomalies, work performed in collaboration with the CIAC (see section of this centers memoir), 7) Collaboration in CIBERER and ISCIII Bio banks Platform research activities and 8) In the field of translational research, involvement in various quality of life and economic impact of patients with Lupus Erythematosus projects, as well as the development of guidelines for clinical practice and analysis of the cost-effectiveness of expanding the neonatal screening program.

Special programs

The IIER maintains the following programs operating: 1) Monitoring a total of 14,518 cases of the Toxic Oil Syndrome cohort, having identified 245 deceased cases during 2015, 2) Collaborating in the development of the population basis screening program for early detection of ASD (TEA in Spanish) in the provinces of Salamanca and Zamora, in collaboration with the University of Salamanca, having screened more than 17,000 children since its inception, and 3) Participation from the Cellular Biotechnology Unit in a Phase I clinical trial (EudraCT: 2008-000364-16; clinicaltrial.gov number: NCT01844661).

Program for cases of undiagnosed rare diseases - SpainUDP

The IIER collaborates with the International Network for Undiagnosed Rare Diseases. This network was created in 2014 and is implementing communication systems for complex cases and opening lines of collaborations between the groups. The IIER relies on a system for case input, procedures for analysis and collaborates with the University Hospital Puerta de Hierro for cases that require specific studies of the clinical phenotype. This program contributes towards both providing diagnostic service as well as research.

National Registry of Rare Diseases

In 2015, the Spain RDR Project period finalized (Spanish Network of Rare Disease Registries for Research <https://spainrdr.isciii.es/>), included in the International Consortium for Research on Rare Diseases (IRDiRC). This Project has established the State Register of Rare Diseases, with more than one million identified cases. It has also published the Royal Decree of the creation of the State Register of Rare Diseases, which will provide sustainability to the action initiated by the Project.

SpainMDB <http://spainmdb.isciii.es> Database of germline mutation

Information system that stores all data on mutations found in Spanish patients affected by rare diseases and cancer.

Training activities and consultancies

The IIER contributes to the postgraduate training of professionals in the field of rare diseases and autism. The IIER has also formed part of the various Expert Committees. The director of IIER is an Independent Expert in the European Commission for Rare Diseases Group and Dr. Eva Bermejo, chief scientist of IIER, is the current president of the Executive Committee of the ICBDSR (International Clearinghouse for Birth Defects Surveillance and Research).

Scientific production

The most important publications are:

Grünewald TG, Bernard V, Gilardi-Hebenstreit P, Raynal V, Surdez D, Aynaud MM. et al. Chimeric EWSR1-FLI1 regulates the Ewing sarcoma susceptibility gene EGR2 via a GGAA-microsatellite. *NatGenet.* 2015 Sep; 47(9):1073-8. doi: 10.1038/ng.3363PMID:26214589

Fernández AF, Bayón GF, Urdinguio RG, Toraño EG, García MG, Carella A et al. H3K4me1 marks regions hypomethylated during aging in human stem and differentiated cells. *Genome Res.* 2015 Jan;25(1):27-40 .doi: 10.1101/gr.169011.113. PMID:25271306

Matamala N, Vargas MT, González-Cámpora R, Miñambres R, Arias JI, Menéndez P et al. Tumor microRNA expression profiling identifies circulating microRNAs for early breast cancer detection. *Clin Chem.* 2015;61(8):1098-106. doi:10.1373 /clinchem. 2015.238691.PMID:26056355

Alfranca A, Martínez-Cruzado L, Tornin J, Abarrategui A, Amaral T, de Alava E et al. Bone microenvironment signals in osteosarcoma development. *Cell Mol Life Sci.* 2015; 72(16):3097-113. doi: 10.1007/s00018-015-1918-y. PMID:25935149

Entrena A, Varas A, Vázquez M, Melen GJ, Fernández-Sevilla LM, García-Castro J et al. Mesenchymal stem cells derived from low risk acute lymphoblastic leukemia patients promote NK cell antitumor activity. *CancerLett.* 2015 Jul 28;363(2):156-65.doi: 10.1016/j.canlet.2015.04.012.PMID:25917077

Matamala N, Martínez MT, Lara B, Pérez L, Vázquez I, Jiménez A et al. Alternative transcripts of the SERPINA1 gene in alpha-1 antitrypsin deficiency. *J Transl Med.* 2015 Jul 4;13:211. doi: 10.1186/s12967-015-0585-y. PMID:26141700

Jiménez-García L, Herránz S, Luque A, Hortelano S. Critical role of p38 MAPK in IL-4-induced alternative activation of peritoneal macrophages. *Eur J Immunol.* 2015 Jan;45(1):273-86. doi: 10.1002/eji.201444806.PMID:25328047

Bladen CL, Salgado D, Monges S, Foncuberta ME, Kekou K, Kosma K et al. The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. *Hum Mutat.* 2015 Apr;36(4):395-402. doi: 10.1002/humu.22758. PMID: 25604253.

Taruscio D, Vittozzi L, Choquet R, Heimdal K, Iskov G, Kodra Y et al. National registries of rare diseases in Europe: an overview of the current situation and experiences. *Public Health Genomics.* 2015;18(1):20-5. doi:10.1159/000365897. PMID:25228300.

Paz S, Torrent J, Poveda JL, Pérez J, Moreno JL, Martín A et al. Experts Consensus on The Future of Rare Diseases Care and Orphan Drugs Access In Spain: A Delphi Study. *ValueHealth.* 2015 Nov;18(7):A679. doi: 10.1016/j.jval.2015.09.2016. PMID: 26533805.

TELEMEDICINE RESEARCH UNIT

The Telemedicine and e-Health Research Unit (UITeS) promotes and develops R+D+i and training in the field of applied ICT for health. The overall objective is the development of “open source” architecture to support environments of collaborative research in m-salud service ecosystems. Its main lines of activity are: a) Development of PITES, Open Platform for Telemedicine and eHealth Innovation, with specific actions in the Active and Assisted Living (AAL) and Mobile Health (mHealth); b) Standardization and interoperability in information systems and electronic health records (EHR); c) Security of Telemedicine Applications d) ICT training (empowerment) in patients and professionals; and e) Evaluation of mobile telehealth e-services.

Scientific-Technical Activities

The main activities in 2015 have been:

- Development and Testing of Telemedicine Services Platform for deployment, proof of concept, pilots and clinical trials. Developed services: Management of content and collaborative work; e-learning for individualized self management training plans; anonymization of clinical information; management of clinical concepts (archetypes); management of EHR extracts.
- Management platform for experimental studies, for methodological support of pilots and clinical trials. Services: Electronic CDR web (based on OpenClinica); randomization; online surveys (based on LimeSurvey); management of educational multimedia content.
- Interoperability platform based on UNE-EN ISO 13606. Services: extracts repository of clinical information; repository of archetypes (concept models); clinical information search; data mining management; pseudonymisation of normalized clinical information; anonymization of standardized information according to UNE-EN ISO 13606.

- Demographic platform. Local and external demographic information server.
- LABTIC. Lab. AAL technologies and Signals and Events Analysis. Audiovisual+usability laboratory. Laboratory for testing devices and connectivity.
- During 2015, 9 research projects were maintained active.

Publications

Lopez-Iturri P, de Miguel-Bilbao S, Aguirre E, Azpilicueta L, Falcone F, Ramos V. Estimation of Radiofrequency Power Leakage from Microwave Ovens for Dosimetric Assessment at Nonionizing Radiation Exposure Levels. *Biomed Res Int.* 2015;2015:603260, doi:10.1155/2015/603260, PMID: 25705676

de Miguel-Bilbao S, Aguirre E, Lopez Iturri P, Azpilicueta L, Roldán J, Falcone F, Ramos V. Evaluation of electromagnetic interference and exposure assessment from s-health solutions based on Wi-Fi devices. *Biomed Res Int.* 2015;2015:784362. doi:10.1155/2015/784362. PMID: 25632400

de Miguel-Bilbao S, García J, Ramos V, Blas J. Assessment of human body influence in exposure measurements of electric field in indoor enclosures. *Bioelectromagnetics* 2015 Feb;36(2):118-32. doi:10.1002/BEM.21888. PMID:25399935

Somolinos R, Muñoz A, Hernando ME, Pascual M, Cáceres J, Sánchez-de-Madariaga R et al. Service for the pseudonymization of electronic healthcare records based on ISO/EN 13606 for the secondary use of information. *IEEE J Biomed Health Inform.* 2015 Nov;19(6):1937-44. doi:10.1109/JBHI.2014.2360546. PMID: 25265637

Moreno Sánchez PA, Garcia Pacheco JL, Charvill J, Lofti A, Langensiepen C, Saunders A et al. iCarer: AAL for the Informal Carers of the Elderly. *Stud Health Technol Inform.* 2015; 210: 678-80. doi: 10.3233/978-1-61499-512-8-678. PMID: 25991237

Ramos Gonzalez V, Jiménez Revolware A. Smart-health, smart-city and power: The life of the new citizen. En: Ortega Esquembre C, Richart Piqueras A, Páramo Valero V, Ruíz Rubio C editores. *Human Improvement, Progress, Research and Ethical and Policy Reflections* Granada: Comares; 2015. p185-93

Sánchez-de-Madariaga R, Muñoz A, Somolinos R, et al. Normalized medical information visualization. *Stud Health Technol Inform.* 2015; 210: 215-17. doi: 10.3233/978-1-61499-512-8-215. PMID: 25991133

Training

Direction of II Master in Management of Systems, Information Technology and Communications for Health. Co-Direction of IX e-Health and Telemedicine meeting, in Summer Courses of the International University of Mendez Pelayo (UIMP).

The UTeS has participated in 8 masters and 4 diploma courses, 19 congresses, 42 seminars, workshops and conferences; directed 1 thesis and participated in 6 courts of theses.

FUNCTIONAL UNIT FOR CHRONIC DISEASE RESEARCH

The mission of the Functional Unit for Chronic Disease Research (UFIEC) is to develop activities in basic and translational research, reference diagnosis and training in chronic diseases, thus becoming a source of scientific-technical support for the most prevalent diseases within the National Health Systems framework. The aim of the UFIEC is to become a Reference Center in Biomedical Research of Chronic Diseases with national and international reach, and a resource of scientific-technical support for the SNS, following the WHO (OMS in Spanish), European Commission, and the Ministry of Health, Social Services and Equality guidelines. The UFIEC currently consists of 12 research and molecular diagnostic reference (human prion) units, also providing transversal services such as the Histology Unit and different platforms that provide the ISCIII with technical support.

Scientific-Technical Activities

UFIEC activities in 2015 have focused on neurodegenerative diseases (Alzheimer's and Parkinson's, lateral amyotrophic sclerosis, multiple sclerosis, prion, etc.), cancer (ovarian, breast, thyroid, lung, colon, nervous system), inflammatory, metabolic and mitochondrial diseases. Aspects of regenerative medicine (stem cells, iPSC), pharmacological targets (signaling, structural models), cell senescence and animal models (premature aging, KO and KO mice, constitutive and inducible) are addressed. UFIEC groups have an important teaching and research training activity. The UFIEC offers high scientific production with numerous articles of excellent impact index in different chronic disease areas.

- Teaching activity: ongoing or completed doctoral thesis (12), Master thesis projects (11), end-of-degree (10), FPII student practices (7) and numerous courses and seminars.
- Molecular diagnostic reference of human Prion (diseases included in the ECDC monitoring program).
- Research support cross services such as the Histology Unit, the optical imaging platform for monitoring in vivo animal models (IVIS), the Luminex platform and the structural analysis of proteins with equipment that provides technical support for the entire ISCIII.

Fundraising

The UFIEC research activity has been financed largely through national (Strategic Action in Health Plan and National Plan Project) and international EU-Joint Programming) competitive funds, as well as scientific-technical support agreements with companies (Servier, Pfizer, Seprox Biotech) and through the collaboration of various institutions and consortia (NEUROSTEM-CM Consortium, BT-CIEN Tissue Bank and CIEN Foundation, Research Institute Hospital "12 Octubre" (i+12), Research Institute Hospital De Paz (IdiPaz), Spanish Neurooncology Research Group, FECMA Federation, Autonomous University of Madrid, Complutense University of Madrid, Francisco de Vitoria University, Thematic Network of Cooperative Cancer Research, CIBERNED, INOC-Contact AICEP Portugal Program, University of the Republic of Uruguay, IIBCE-Ministry of Education and Culture of Uruguay). In 2015, all UFIEC units have had at least one active project in competitive summons. The total number of activities associated to projects, contracts and active agreements was of 18.

Scientific Production

Publication of 27 papers in international journals, more than 23 congress communications and 2 patent applications. Some of the most important publications in 2015 were:

Andreu Z, Khan MA, González-Gómez P, Negueruela S, Hortigüela R, San Emeterio J, et al. The cyclin-dependent kinase inhibitor p27 kip1 regulates radial stem cell quiescence and neurogenesis in the adult hippocampus. *StemCells* 2015 Jan;33(1):219-29. doi: 10.1002/stem.1832. PMID: 25185890

González-Gómez P, Crecente-Campo J, Zahonero C, de la Fuente M, Hernández-Laín A, Mira H et al. Controlled release microspheres loaded with BMP7 suppress primary tumors from human glioblastoma. *Oncotarget* 2015 May 10;6(13):10950-63. PMID: 25860932.

López-Alonso V, Ortiz S, Martínez-Suárez JV. Genome sequences of five disinfectant-resistant *Listeria monocytogenes* strains from two Iberian pork-processing plants. *Genome Announc* 2015 Mar 5;3(2). pii:e00077-15. doi: 10.1128/genomeA.00077-15. PMID: 25745005.

Mineev KS, Goncharuk SA, Kuzmichev PK, Vilar M, Arseniev AS. NMR Dynamics of Transmembrane and Intracellular Domains of p75NTR in Lipid-Protein Nanodiscs. *Biophys J*. 2015 Aug 18;109(4):772-82. doi:10.1016/j.bpj.2015.07.009. PMID: 26287629.

Olazarán J, Gil-de-Gómez L, Rodríguez-Martín A, Valentí-Soler M, Frades-Payo B, Marín-Muñoz J et al. A blood-based, 7-metabolite signature for the early diag-

nosis of Alzheimer's disease. *J Alzheimers Dis*. 2015; 45(4):1157-73. doi: 10.3233/JAD-142925. PMID: 25649659.

Quintana E, Fernández A, Velasco P, de Andrés B, Liste I, Sancho D et al. DNGR-1+ dendritic cells are located in meningeal membrane and choroid plexus of the non injured brain. *Glia* 2015 Dec;63(12):2231-48. doi: 10.1002/glia.22889. PMID:26184558.

Zahonero C, Aguilera P, Ramírez-Castilejo C, Pajares M, Bolós MV, Cantero D et al. Preclinical test of Dacomitinib, an irreversible EGFR inhibitor, confirms its effectiveness in glioblastoma. *Mol Cancer Ther* 2015 Jul; 14(7): 1548-58. doi: 10.1158/1535-7163.MCT-14-0736. PMID: 25939761.

HEALTH CARE RESEARCH UNIT INVESTÉN-ISCIII

The Health Care Research Unit works towards promoting research in nursing care and other disciplines related to this field. The mission of the Unit is to develop a national strategy to promote and coordinate translational and multidisciplinary care research, enhancing its integration into daily clinical practice in order to achieve the highest quality of care based on valid and reliable results that stem from research.

Obtained milestones or achievements:

- Inception of the inter-university collaboration Doctorate between the University of Jaén, University of Balearic Islands, University of Lleida, University of Vic and the ISCIII.
- Participation in 10 national and international consortia.
- Leader of the European Region of the Joanna Briggs Institute in 2015.
- Esther González María y Gema Escobar Aguilar obtaining the title of Doctor.
- Recognition for the collaboration with the Spanish Federation of Parents of children with Cancer.

Scientific-Technical Activities

- Collaboration agreements with 16 CCAA (Autonomous Communities) and two international institutions.
- Elaboration of the 2016-2020 Unit strategic plan.
- Conference "Support for research use in organizations and health systems. Transfer of knowledge to management". Dr. John Lavis MD (Queens), MSc (LSE), PhD (Harvard).

- Organizing and Scientific Committee. Sharing Good Practices to improve Quality of Care and Patient Safety (PasQ). Ministry of Health, Social Services and Equality.
- Organization of the XIX International Meeting of Research in Care.
- Organization of the online courses: "Research Methodology Applied to Health Care" and "Clinical Practice Base don Evidence".
- 9 national and international active projects.

Scientific Production

Batinga H, Martinez-Nicolas A, Zornoza-Moreno M, Sánchez-Solis M, Larqué E, Mondéjar MT et al. Ontogeny and aging of the distal skin temperature rhythm in humans. *Age (Dordr)*. 2015;37(2):29. doi: 10.1007/s11357-015-9768-y. PMID:25813804

Ramos-Morcillo AJ, Ruzafa-Martínez M, Fernández-Salazar S, del-Pino-Casado R. Elderly Roma womens expectations and experiences of primary care service use. *Aten Primaria*. 2015 Apr;47(4):213–9. doi: 10.1016/j.aprim.2014.05.011. PMID:25155896

Moreno-Martínez FJ, Ruzafa-Martínez M, Ramos-Morcillo AJ, Gómez-García CI, Hernández-Susarte AM. Design and validation of a questionnaire on childhood knowledge and personal hygiene habits (HICORIN®). *Aten Primaria*; 2015 Aug-Sep;47(7):419–27. doi: 10.1016/j.aprim.2014.10.004. PMID:25559566

Ramos-Morcillo AJ, Fernández-Salazar S, Ruzafa-Martínez M, del-Pino-casado R. Effectiveness of a Brief, Basic Evidence-Based Practice Course for Clinical Nurses. *Worldviews Evid Based Nurs*. 2015 Aug;12(4):199–207. doi: 10.1111/wvn.12103. PMID:26220505

Abad E, Molina F, Pérez A, et al Vivo MC. Evaluation of the implementation of the health training program on life support. *FEM* 2015; 18 (S2): S73, resumen

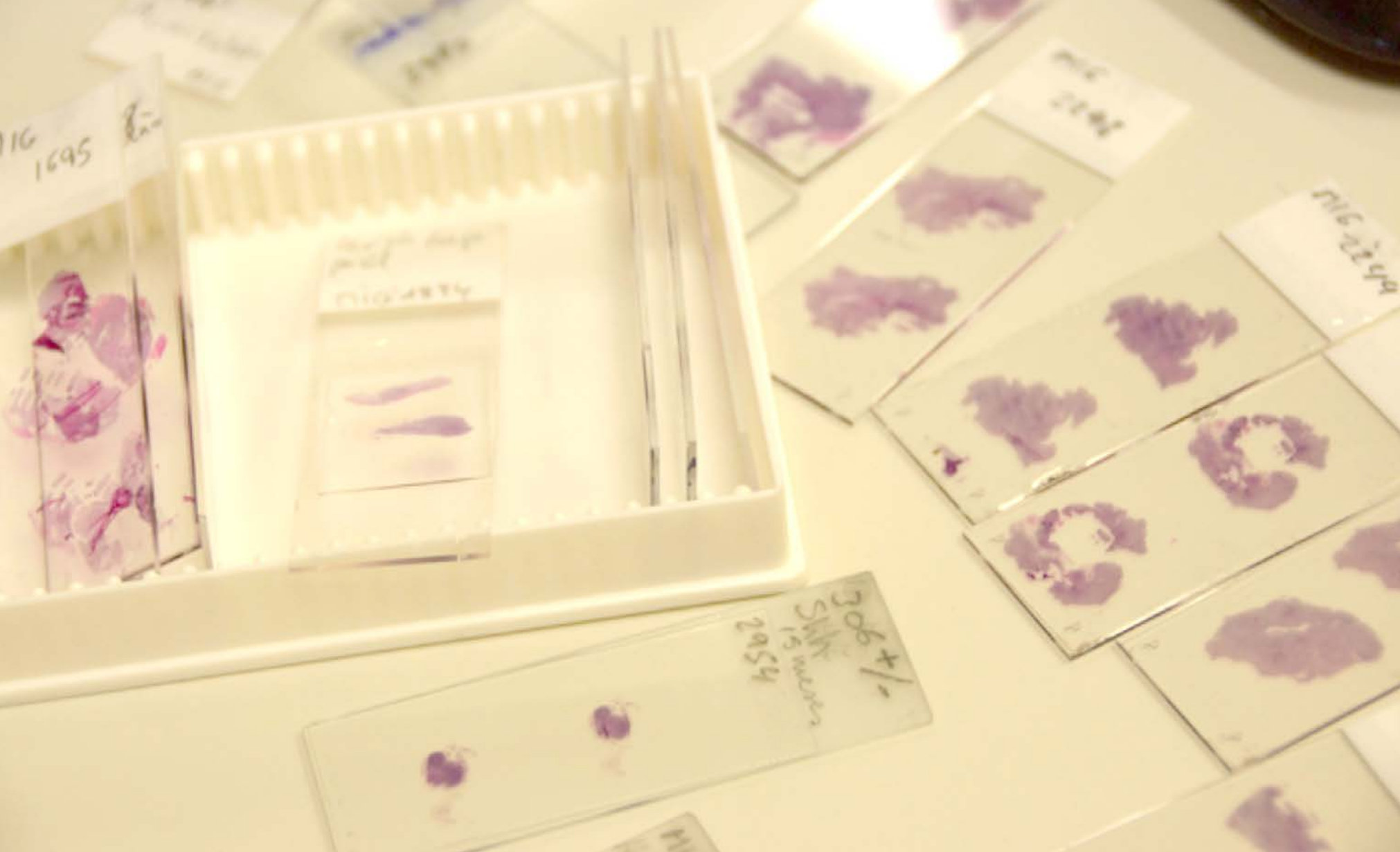
Molina F, Abad E, Serrano P, et al. A regional experience of assesing the relevance of continued education. *FEM* 2015; 18 (S2): S72, resumen

Lapeña-Moñux Y R, Cibanal-Juan L, Maciá-Soler ML, Orts-Cortés MI, Pedraz-Marcos A. Interpersonal relations and nurses' job satisfaction through knowledge and usage of relational skills. *Appl Nurs Res*. 2015 Nov; 28(4):257-61. doi:10.1016/j.apnr.2015.01.009. PMID:26608422

Ramalle-Gómara E, Ruiz E, Quiñones C, Andrés S, Iruzubieta J, Gil-de-Gómez J. General knowledge and opinion of future health care and non-health care professionals on rare diseases. *J Eval Clin Pract*. 2015 Apr; 21(2):198-201. doi: 10.1111/jep.12281. PMID:25363689

Albornos-Muñoz L, González-María E, Moreno-Casbas T. Implementation of good practice guidelines in Spain. Program of Centers committed to excellence in care. *MedUNAB*. 2015;17(3):163-69.





NETWORK OF BIOLOGICAL ALERT LABORATORIES, RE-LAB

The Network of Biological Alert Laboratories (RE-LAB) was created through the Ministerial Order PRE/305/2009, of February 10th, and modified through the Order PRE/2565/2015, of November 26th, as an Infrastructure for scientific-technical operative support towards the National System for Conducting Crisis Situations, for responding to dangerous biological agent threats.

Scientific-Technical Activities

The RE-LAB Management Unit has coordinated a laboratory response to postal consignment alerts containing possible biological warfare recorded throughout the year in various public institutions and private entities of national territory.

As coordinator of the RE-LAV, the ISCIII is part of the National Working Group for the Implementation of the Nuclear, Radiological, Biological and Chemical Action Plan (NRBQ) of the European Union, coordinated by the Department of Homeland Security of the Prime Minister's office. The ISCIII also leads the National Working Subgroup of Biological Affairs of the NRBQ Action Plan.

A representative of the RE-LAB Management Unit is part of the Interministerial Group for Biological and Toxin Weapons (GRUPABI), coordinated by the General Sub direction of Non-Proliferation and Disarmament of the Ministry of Foreign Affairs and Cooperation (MAEC), has participated in group meetings and has coordinated the information provided by the RE-LAB laboratories for the Spanish declaration of trust development measures in the Convention for the Prohibition of Biological Weapons.

Conversely, the ISCIII participates in the Inter-ministerial Contact Group of the 1540 Resolution of the United Nations Security Council coordinated by the MAEC.

Fundraising

The ISCII has coordinated the "Iberian network of laboratories of biological alert. Accreditation of methods for detection of highly pathogenic agents, IB-BIOALERTNET" project, funded by the Department of Interior (DG HOME) of the European Commission.

Training

Participation in various specialization courses in TEDAX-NRBQ organized by the Forces and Bodies of State Security as well as courses, workshops and seminars organized by the Center for Legal Studies of the Ministry of Justice, Ministry of Foreign Affairs and Cooperation and the National Institute of Health Dr. Ricardo Jorge de Lisboa.

NATIONAL BANK OF CELL LINES

The national bank of cell lines is a bio bank network with nodes in Granada, Barcelona, Valencia and San Sebastian that provides the scientific community with all of the stem cell lines that are derived in our country. The directorate resides in the Sub direction of Cell Therapy and Regenerative Medicine, and the role of chairman and secretary of the Technical Commission thereof (RD 590/2005, of May 20th, approving the modification of the Carlos III Institute of Health Statute.

In 2015 (July) the appointing of Ms. Victoria Ureña Vilardell took place as Director of the National Stem Cell Bank and President of the Technical Commission in place of D. Javier Arias Díaz.

Relation of deposited lines during 2015

The following have been deposited in the BNLC during 2015: 4 embryonic cell lines generated in the Andalusia Node and 16 induced pluripotent lines (iPS).

iPS lines: 8 have been developed by the Barcelona Node, 4 by the Josep Carreras Leukemia Research Institute (IJC), 3 by the Biodonostia Institute/ IBEC and 1 by the Pfizer Center-University of Granada-Andalusian Council of Genomics and Oncological Research (GENYO).

Requested lines

During 2015 the ceding of 11 cellular lines were requested and approved for 6 projects belonging to 6 researchers.

Embryonic lines: 4 lines: (VAL-3), VAL-4, VAL 5, VAL-9 for 2 projects.

iPS lines: 6 lines: FiPS-4F-7, FiPS-4F-8, iPS0989#2f, iPS0924#6, iPS0826#6, CBiPS1sv-4F-5, for three projects.

Adult cell lines: 1 (bone marrow mesenchymal stem cells) for 1 project.

International Projection

8TH INNOVATIVE MEDICINES INITIATIVE (IMI) (PROJECT NUMBER 115582-3)

Title: European Bank for induced pluripotent Stem Cells (EBISC)

Participation in National Research Platforms.

The nodes of the National Bank of Cell Lines participate in the Biomolecular and Bioinformatics Resource Platform (PRB2).

RESEARCH RESULTS TRANSFER OFFICE (OTRI)

The direction and coordination of research result transfer activities corresponds to the OTRI. The following are among the major outstanding activities in 2015:

Patent Management

In 2015, we dispose of an asset portfolio of 57 patents (granted and applied for), 25 of them national (Spanish) and 32 foreign, with a total of 26 priority or patent families. Processed patent applications include:

- Methods for Apo lipoprotein detection.
- Use of mesothelial cells in tissue bioengineering and artificial tissues
- Method for obtaining pancreatic beta cell surrogates by increasing pancreatic and duodenal homeobox 1 (pdx) expression.
- Use of cord blood plasma to treat NK cell-mediated diseases and IFN-gamma mediated diseases.
- Nano particulate systems for in vitro transfection.
- Insulator to improve gene transfer vectors.
- New p-terphenyls hexakis-substituted with bilateral groups for treatments of infection by HIV type 1 virus (HIV-1) and other diseases.
- Raman, infrared, or infrared-Raman analysis of peripheral blood plasma protein structure and its relationship to cognitive development in Alzheimer's disease.
- Lentiviral vector of self-limited expression.
- Kit and method for detecting and quantifying natural variants of the hepatitis C virus, genotype 1, subtype a), that compromise the Q80K mutation.

The last two patents are 100% owned by the ISCIII and the rest are under shared ownership with other institutions. Overall, 13 have been national applications in foreign countries in face of the European Patent Office, 4 have been international PCT applications and 2 have been national priority applications in Spain.

Patent, Material, Know-How Licenses

The "Methods for apolipoprotein detection" patent presented in the European Patent Office has been licensed to the company Biocross, S.L., who is also

co-owner of the patent along with ISCIII and Ciberned. Several international agreements have also been processed for transferring and licensing the use of materials.

Technology-based companies

During 2015 the ISCIII governing council approved the Institutes participation in technology-based company Virnostica, S.L.'s social capital.

Dissemination of Technologic Offer: Assistance in Fairs and Congresses

The OTRI actively participated in TRANSFIERE, the European Science, Technology and Innovation Forum held in Malaga, where the Institutes scientific-technical offer was disseminated and meetings with companies in the sector were maintained. In addition, technological offer dissemination activities were carried out through emailing and technological portals such as the EEN (Enterprise Europe Network) or the ISCIII website.

Other activities: Consultancy and advising

Consultancy and advising endeavors have been undertaken regarding consultations made by ISCIII researchers on research result patentability, processing of various types of documents, such as internal ISCIII procedures, and regulatory projects, highlighting the Legislative Royal Decree, with which the Restated Text of the Law of guarantees and rational use of medicine and medical products was approved.

SCIENTIFIC CULTURE AND INNOVATION UNIT (UCCIII+i)

Established at the end of 2014, the UCIII+i aims towards promoting scientific culture and innovation in our society in health, biomedicine and environmental health. During 2015, the UCCII+i performed a series of activities geared towards consolidating and preparing the Units future activities. In 2015 the Unit participated in conducting ISCIII scientific camps, an activity performed with children aged 6 to 12 during the summer holiday and that pursues stimulating their interest in science and research, particularly related to biomedicine. The Unit has also participated in the FECYT aid summons, resulting as beneficiary of an aid to conduct a series of activities related to the units goals in 2016.

HEALTH TECHNOLOGY ASSESSMENT AGENCY (AETS)

The Health Technology Assessment Agency addresses the information and scientific evidence needs of the National Health System regarding the definition of its policies for providing health benefits and improving quality and efficiency. For this purpose, it provides objective assessment of the health, social ethical, organizational and economic impact of health techniques, procedures and practices in order to provide a scientific basis for decision making by the authorities and other healthcare agents. Since 2012, a portion of the AETS technical services is a part of the "Spanish Network of Health Technology Assessment and Performance of the National Health System Agencies".

Scientific-Technical Activities

The following have been performed during 2015: 1) 14 health technology assessment reports, 2) 2 monitoring studies on technologies, techniques and procedures 3) 5 technical specification sheets on new and emerging health technologies.

4 new research projects have been initiated and 5 pre-existing research projects have been continued.

Scientific Production

Amate JM, López-Cuadrado T, Almendro N, Bouza C, Saz-Parkinson Z, Rivas-Ruiz R, Gonzalez-Canudas J. Effectiveness and safety of glimepiride and iDPP4, associated with metformin in second line pharmacotherapy of type 2 diabetes mellitus: systematic review and meta-analysis. *Int J Clin. Pract.* 2015 Mar;69(3): 292-304. doi: 10.1111/ijcp.12605. PMID: 25683794.

Bouza C, López-Cuadrado T, Almendro N, Amate JM. Safety of balloon kyphoplasty in the treatment of osteoporotic vertebral compression fractures in Europe: a meta-analysis of randomized controlled trials. *Eur. Spine J.* 2015 Apr;24(4):715-23. doi: 10.1007/s00586-014-3581-7. PMID: 25399304

García-Pérez L, Pinilla-Domínguez P, García-Quintana A, Caballero-Dorta E, García-García FJ, Linertová R, Imaz-Iglesia I. Economic evaluations of implantable cardioverter defibrillators: a systematic review. *Eur J Health Econ.* 2015 Nov;16(8): 879-93. doi: 10.1007/s10198-014-0637-x. PMID: 25323413.

Hernández Torres A, García Pellicer MP, García Matas A, Tejero García P, García Matas MC, Modrego Aznar F. Improving quality of life in patients with venous disease, treated in a protocolized way with natural antioxidant peloids as vascular adjuvants. *Balnea* 2015 (10); 342-344.

Imaz-Iglesia I, García-San Miguel L, Ayala-Morillas LE, García-Pérez L, González-Enríquez J, Blasco-Hernández T, Martín-Águeda MB, Sarría-Santamera A. Economic Evaluation of Chagas Disease Screening in Spain. *Acta Trop*. 2015 Aug; 148: 77-88. doi: 10.1016/j.actatropica.2015.04.014. PMID: 25917718.

Medel-Herrero A, Amate JM, Saz-Parkinson Z, Gomez-Beneyto M. Changing trends in hospitalization rates associated with psychosis: Spain, 1980-2009. *Soc. Psychiatry Psychiatr. Epidemiol*. 2015 Dec;50(12):1843-55. doi: 10.1007/s00127-015-1128-9. PMID: 26415493.

Sánchez-Gómez LM, Polo-deSantos M, Gómez-Sancha F, Luengo-Matos S. Efficacy and safety of the UROLIFT® system for the treatment of benign prostatic hyperplasia symptoms: a systematic review. *Actas Urol Esp*. 2015; 39 (5): 311-9. doi:10.1016/j.acuro.2014.05.010. PMID: 25260950

Sánchez-Gómez LM, Polo-deSantos M, Rodríguez Melcón JI, Angulo JC, Luengo-Matos S. Hypofractionalized radiotherapy versus conventional radiotherapy in prostate cancer: a systematic review of efficacy and safety. *Actas Urol Esp*. 2015 Jul-Aug; 39(6): 367-74. doi: 10.1016/j.acuro.2014.12.005. PMID: 25660427

Sarría-Santamera A, Prado-Galbarro FJ, Martín-Martínez MA, Carmona R, Gamiño Arroyo AE, Sánchez-Piedra C, Garrido Elustondo S, del Cura González I. [Survival of patients with heart failure in primary care]. *Aten Primaria*. 2015 Aug-Sep;47(7):438-45. PubMed PMID: 25487462.

Sarría Santamera A, Prado Galbarro J, Quintana Díaz M, Martínez Virto A. Determinants of the use of emergency services in Spain. *Primary Care*. 2015 Jun-Jul;47(6):386-8. doi: 10.1016/j.aprim.2014.09.011. PMID: 25573446.

Sarría-Santamera A, Prado-Galbarro J, Ramallo-Farina Y, Quintana-Díaz M, Martínez-Virto A, Serrano-Aguilar P. Use of emergency services in rural and urban areas in Spain. *Semergen*. 2015 Mar;41(2):63-9. doi: 10.1016/j.semerg.2014.02.006. PMID: 24726281.

JOINT CENTER FOR HUMAN EVOLUTION AND BEHAVIORAL RESEARCH (ISCIII-UCM)

Ancient DNA

The dynamics of human populations in the change from Pleistocene to Holocene are one of the main lines of research that have been carried out. One of the studies results, conducted in collaboration with an international team, propose a single (single wave) origin and a maximum antiquity of 23,000 years for the first settlers of the New World. Raghavan M, Steinrucken M, Harris K, Schiffels S, Rasmussen S, DeGiorgio M, et al. Genomic evidence for the Pleistocene and recent population history of Native Americans. *Science*. 2015 Aug 21; 349(6250):aab3884–aab3884. DOI: 10.1126/science.aab3884

In addition, regarding the genetic identity of the first farmers in the Atapuerca site of Portalón, the contribution of individuals from the Near East and their infusion with local people through time, has been determined. Günther T, Valdiosera C, Malmström H, Ureña I, Rodríguez-Varela R, Sverrisdóttir ÓO, et al. Ancient genomes link early farmers from Atapuerca in Spain to modern-day Basques. *Proceedings of the National Academy of Sciences*. 2015 Sep 22; 112(38):11917–22. DOI: 10.1073/pnas.1509851112

Moreover, the two published papers on the Iberian lynx expand its range of distribution to Italy, by demonstrating that the *Lynx spalaeus* is an Iberian lynx of greater size. Also demonstrated genetically for the first time, the presence of the boreal lynx in Spain, thus closing a long debate.

Two doctoral theses have also been defended: Ureña Herradón, I. (2015). Paleogenetics of the Pyrenean ibex and the alpine ibex: A micro evolutionary study. UCM, Faculty of Biology. Rodríguez Varela, R. (2015). Variations in the distribution and genetic structure from the Upper Pleistocene of Palearctic lynx and the Vole of Cabrera. UCM, Faculty of Geology.

Cognitive Neuroscience

During 2015 a new line of research has been addressed related to exploring the neurocognitive processes involved in assessing haute cuisine experiences, in collaboration with the Mugartiz restaurant in San Sebastian. In addition, further work on aspects of human language and its relation to other cognitive processes continues.

As main pathology, schizophrenia is studied due to its implications regarding a large array of conducts in human behavior.

Neurophysiological mechanisms of human behavior are addressed through pathology and normality in order to understand its origins, its development and evolution, and avoid its possible alterations.

Scientific Production

Out of the 5 articles that have been published, the following are highlighted:

Muñoz, F.; Martín-Loeches, M. Electrophysiological brain dynamics during aesthetic judgment of human bodies and faces. *Brain Res.* 2015 Jan 12;1594:154-64. doi:10.1016/j.brainres.2014.10.061. PMID: 25451119

Bruner E, Román, FJ, de la Cuétara JM, Martín-Loeches M, Colom R. Cortical surface area and cortical thickness in the precuneus of adult humans. *Neuroscience.* 2015 Feb 12; 286:345-52. doi: 10.1016/j.neuroscience.2014.11.063. PMID: 25499315

Human Evolution

Out of the more than sixty articles published in this annuity, highlights include the publication of the largest postcranial skeleton collection of a fossil species of the last million years, the first case of interpersonal violence and the identification of Phillip II of Macedonia, father of Alexander the Great.

The most complete characterization of Middle Pleistocene bones was presented in the *Journal of the Academy of Sciences of The United States (PNAS)*, based on the study of the human postcranial skeleton from the Pit of Bones (Sima de los Huesos) in Atapuerca. Through this collection made up of more than 1500 bones, the best approach has been achieved for determining the size and shape of the genus *Homo* skeleton during the last million years before the appearance of modern humans and its paleobiological implications. Furthermore, based on the anatomical and functional design, four major phases of human evolution can be described.

The study of skull 17 of the Pit of Bones (Sima de los Huesos), published in the *Journal of Archeological Science*, has provided the earliest evidence of interpersonal violence in the fossil record of hominids, in other words, a murder that was committed 430,000 years ago. Two blunt skull injuries affect both the outer and inner surface, with almost identical dimensions and counters that suggest that they were caused by the same object. The differences in the trajectories indicate that each lesion was caused by a different blow.

The study of human remains corresponding to an adult man, a young woman and a newborn that proceed from grave I of Vergina (Greece) was also presented in *PNAS*. The research results, based largely on the study of severe pathologies presented by the male individual, explains the “mystery” of the Macedonian Royal Tombs, a “mystery” that historians, archaeologists and anthropologists have faced for nearly forty years.

Divulgation

Three temporary exhibitions in the Museum of Human Evolution (Burgos): The Sima de Los Osos (The Pit of Bones), They went with the wind. The sixth extinction and Txalupak & carts.

RESEARCH CENTER FOR THE STUDY OF CONGENITAL ANOMALIES (CIAC)

The Research Center for the Study of Congenital Anomalies (CIAC) under the Institute of Health Carlos III carries out its ECEMC activity (scientific group of ASEREMAC – Spanish Association for Registration and Study of Congenital Malformations) under the framework agreement reached with the Institute of Health Carlos III, following the creation of the ISCIII-ASEREMAC Joint Center. The ECEMC (Spanish Collaborative Study on Congenital Malformations) is a program for clinical and epidemiological research on birth defects, with a multidisciplinary and translational approach. The ECEMC is structured as a thematic network of cooperative research. It's based on a permanent registration system of newborns with case-control birth defects, based in hospitals. The group is part of the Center for Biomedical Network Research on Rare Diseases (CIBERER) since its constitution in 2006, and is also integrated into the following international networks: ICBDSR (International Clearinghouse for Birth Defects Surveillance and Research –www.icbdsr.org), EUROCAT (European Surveillance of Congenital Anomalies –www.eurocat-network.eu), and ENTIS (European Network of Teratology Information Services –www.entis-org.eu).

Scientific-Technical Activities

ECEMC clinical network maintenance, clinical dysmorphology evaluation on more than 1,016 newborns and fetuses with birth defects in Spain.

Cytogenetic study (high resolution and molecular): 155 samples (ECEMC environment).

Attention to 501 medical consultations made to SITTE (Spanish Telephone Information Service on Teratology) and 2,148 made to SITE (Telephone Information Service for Pregnant Women).

DC Epidemiological Surveillance in Spain, in EURCAT Europe (www.eurocat-network.eu) and worldwide within the ICBDSR (www.icbdsr.org), whose Executive Committee is presided over.

Participation in the organization of the first World Birth Defects Day (March 3).

Commencement of a project on descriptive aspects and genotype-phenotype correlation in patients with 5p syndrome. IP: M.L. Martínez-Frías.

Publication of 3 “Propositus: ECEMC Fact Sheets” in <http://www.fundacion1000.es/boletines-ecemc>

Other Activities

Organization of the: “XXXVIII ECEMC Annual Meeting” and “Update Course on DC Research”. Avilés, 16/October-17-2015 [2,2 credits CFPCS Comunidad of Madrid-SNS. Expte. 07-AFOC-04710.2/2015].

Participation in the organization of the “42nd Annual Meeting of the ICBDSP”, Spoleto (Italia), 10/september-14-2015.

Two editions of the “Conference of Clinical Teratology”. Organized by the Ministry of Health of Castilla and Leon and the CIAC. Valladolid and Palencia.

Official Master training in “Current Knowledge on Rare Diseases”, International University of Andalucia and in the Higher Diploma of “Food, Nutrition and Public Health-Clinical Nutrition Module”.

Scientific Production

Arroyo-Carrera I, de Zaldívar Tristancho MS, Bermejo-Sánchez E, Martínez-Fernández ML, López-Lafuente A, MacDonald A et al. Deletion 1q43-44 in a patient with clinical diagnosis of Warburg-Micro syndrome. *Am J Med Genet A*. 2015 Jun;167(6): 1243-51. doi: 10.1002/ajmg.a.36878. PMID: 25899426

Marchegiani S, Davis T, Tessadori F, van Haaften G, Brancati F, Hoischen A, et al. Recurrent mutations in the basic domain of TWIST2 cause AblepharonMacrostomia and Barber-Say Syndromes. *Am J Hum Genet*. 2015 Jul;97(1):99-110. doi: 10.1016/j.ajhg.2015.05.017. PMID: 26119818

Martinez F, Marín-Reina P, Sanchis-Calvo A, Perez-Aytés A, Oltra S, Roselló M et al. Novel mutations of NFIX gene causing Marshall-Smith syndrome or Sotos-like syndrome: one gene, two phenotypes. *Pediatr Res*. 2015 Nov;78(5):533-9. doi: 10.1038/pr.2015.135. PMID: 26200704

Martínez-Fernández ML, Fernández-Toral J, Llano-Rivas I, Bermejo-Sánchez E, MacDonald A, Martínez-Frías ML. Delineation of the clinically recognizable 17q22 contiguous gene deletion syndrome in a patient carrying the smallest microdeletion known to date. *Am J Med Genet A*. 2015 Sep; 167A(9):2034-41. doi: 10.1002/ajmg.a.37117. PMID: 25899082

NATIONAL LIBRARY OF HEALTH SCIENCES

The National Library of Health Sciences (BNCS) was established as a National Center of the Institute of Health Carlos III on August 2, 1996 (Royal Decree 1893/1996), and acts as a management and coordination hub for all of the Institutes libraries. Moreover, the BNCS renders its services to the National Health System, providing documentary support and serving as a reference center on a wide range of topics related to scientific health information for all the health administrative units at central and regional level.

Dissemination Initiatives of Spanish Scientific Information

1. Virtual Health Library-Spain (<http://bvsalud.isciii.es>)

Since its introduction in 2001, the Virtual Health Library in Spain (BVS) is a part of the International Network of Virtual Health Libraries. This Network currently relies on the participation of 30 Latin American countries, Africa and Asia. It consists of more than 90 national virtual, thematic and institutional Libraries and is coordinated by BIREME (Latin American and Caribbean Center on Health Science Information)

During 2015, the BVS Spain portal has migrated to a new platform, updating content and adding a search bar for topics and BVS Network available resources. BVS Spain provides access to the following documental products:

1.1 IBECS Spanish Bibliographic Index of Health Sciences (<http://ibecs.isciii.es>)

226 indexed Spanish biomedical journals

143.714 articles (An increase of more than 12,390 registers compared to 2014)

23.234 links to the full text of articles included in SciELO Spain

1.2 SciELO Spain- Scientific Electronic Library Online (<http://scielo.isciii.es>)

59 publications (3 new titles added in 2015)

More than 30.000 full text articles (html y pdf)

More than 9,8 million visits and more than 23 million downloaded pages

The SciELO Spain page accounts for 88.20% of ISCIII web traffic

Integrated in Web of Science (WoS) through the SciELO Citation Index

Presence in Google Scholar

Presence in open Access directories: Hispana/DOAJ/OAISTER/ROAR

27th position in the world ranking of Webometrics portals

1,054 DOI articles deposited in CrossRef in 2015

1.3 LIS-Spain Health Information Locator

Compilation of quality health sites

2,345 records in Information for the professional

1,915 records in Information for citizens

1.4 DeCS Health Sciences Descriptors

Adaptation of the trilingual thesaurus to Spanish used in Spain (ES/EN/PT) of biomedical terms elaborated by BIREME from the MeSH of the National Library of Medicine

Translation of 438 new terms

Translation of 53 modified terms

Translation review of 1,524 existing terms

2. CNCS National Catalogue of Health Sciences

140,000 bibliographic records of 287 libraries

Loaded information of 19,194 magazines

Integrated 67,927 paper funds and 382,377 electronic funds

3. Social Networks BNCS National Library for Health Sciences d

Corporate Twitter (@BNCSisciii) 225 followers

SciELO Spain Twitter (@scielospain) 3.3K followers

BVS Spain Twitter (@bvs_spain) 2K followers

BVS Spain Facebook (www.facebook.com/BVSSpain)

Corporate Pinterest c (<https://es.pinterest.com/bncsalud>)

Library Services

The BNCS provides ISCIII researchers, National School of Health and Occupational Medicine students and any accredited research user, such a researchers, teachers or NHS health professionals with coverage. In 2015, 1,920 visits to the two reading rooms were recorded (Majadahonda Campus and Chamartin Campus). The library manages bibliographical collections constituted by 41,041 publications, of which 36,565 are monographs, 2,950 are periodical publications and the audiovisual material. Out of the total number of periodical publications, 329 are active subscriptions of the most important scientific editors in the field of Health Sciences. During 2015, 650 publications were catalogued, and 470 book loans have been recorded. Within the ISCIII collaboration agreement

with the CNIC and CNIO foundations, online joint access is provided of 911 titles (journals, monographic series and electronic books.) There have also been more than 75,000 hits registered on full text of books and electronic journals.

91,945 bibliographical searches have been registered in data bases directly subscribed to by BNCS, such as Web of Science (86%), SCOPUS (8%) or the Journal Citation Reports (5%).

In 2015, the interlibrary loan service and documents request handled 10,087 requests, 4,971 of which were from ISCIII researchers and 5,116 from Spanish academic libraries and the health system.

Editorial Program

13 monographs and 2 periodical publications have been edited in electronic form, as well as a bilingual Spanish/English corporate brochure in printed form. Free access to all electronic publications edited by the ISCIII starting from 2009 can be found through the web address <http://publicaciones.isciii.es/> The portal has user alert system with 2,147 registered subscribers.

Museum of Health and Public Hygiene

494 anatomical parts have been catalogued as well as 441 photographic records of autopsies performed at the Hospital del Rey from 1925 to 1957. 11 guided tours were carried out for groups of professionals, students and people interested in the history of public health in Spain.

Collaborations

An association agreement has been reached between the Institute of Health Carlos III, through the BNCS, and BioMed Central (BMC) to actively support open access publishing and contribute to the guarantee of dissemination of scientific literature produced in the institution. A Framework Agreement has been formalized for a period of 4 years between the ISCIII and the CNIC and CNIO foundations to facilitate collaboration between documentation and library services and joint access to resources of common interest.

Training

The National Library of Health Sciences has conducted scientific documentation modules in various diploma, expert and master courses in the ENS, ENMT, UNED and Community of Madrid. In addition, PubMed and Scientific Information workshops were conducted within the ISCIII internal personnel network.

Publications and Conferences

Elena Primo Peña. Databases of biomedical documentation in Spanish: present and future (conference). X MEDES SESSION 2015 Scientific knowledge and communication. Complutense Summer Courses in El Escorial, July 2015

Elena Primo Peña, member of the scientific committee of the 1st Bibliosalud Meeting ICOMEM, Madrid May 22, 2015.

Elena Primo Peña. Health information for citizens on the Internet: documentary participation. Seminar. Sources of information on health and citizenship. Complutense University, October 2015.

3.2 Intramural Research

Intramural research is performed within the Institute of Health Carlos III (ISCIII) centers and mixed units that are associated through the execution and development of competitive research projects, management packages and collaboration agreements. Funding resources of the mentioned competitive projects are diverse in nature: I+D+I National Plan Programs, of the Strategic Action in Health (AES) within the ISCII Intramural Research Program and other regional, national and international public and/or private summons.

The data presented in this section gathers the scientific production results of the ISCII centers and schools through diverse studies and indicators: analysis of scientific publications, technologic transfer, research projects and hiring of research and support staff.

This information has been collected and analyzed through the Research Coordination Area (ACI).

RESEARCH COORDINATION AREA

The Research Coordination Area (ACI) aims towards managing and coordinating research-related activities conducted at the ISCII within the context of national and international research summons. It is under the authority of the Sub-Directorate of General Services, Training and Research and its primary functions include promoting grant summons for funding projects and human resources, advising researchers in the preparation and presentation of proposals, and the management of national and international projects, agreements, contracts and assignments, their monitoring and justification. Monitoring and justification of grants towards hiring research staff and economic monitoring and statistical analysis of the intramural research situation.

2015 Summon Projects Granted by Program

Financing	Program	N° Projects	Total Fianancing
External Funding	International Agreements *	12**	1.008.735,89
	National R+D+I Plan	8	1.110.000,00
	Other	5	516.599,00
ISCIII Funding	AESI	20	1.708.895,90
	Other	1	144.823,00
TOTAL		46	4.489.053,79

* UE, ECDC, etc | ** 8 projects and 4 sub-projects

2015 Current Projects by Program

Financing	Program	N° Projects	Financing Total	2015
External Funding	International Agreements* 56**		11.483.435,9	13.200.012,23
	National Plan R+D+I	27	4.234.465,83	1.498.523,98
	Ministry of Health	2	231.220,00	24.431,64
	Autonomous Regions	6	379.543,41	94.657,77
	Other	8	718.880,73	205.962,75
ISCIII Funding	FIS	83	9.664.714,84	2.116.909,12
	AESI	23	1.987.526,12	325.273,53
	Networks	21	2.257.903,86	913.024,93
	Other	36	1.942.135,57	583.750,78
TOTAL		264	32.899.826,27	8.962.546,73

* UE, OMS, ECDC, etc | ** 37 projects and 19 sub-projects

Granted Projects by Subject Area. 2015

Subject Area	N° Projects
Infectious Diseases: Bacteriology	4
Infectious Diseases: Mycology	1
Infectious Diseases: Parasitology	2
Infectious Diseases: Virology	6
Neurologic Diseases	3
Rare Diseases	2
Epidemiology of Infectious Diseases	3
Epidemiology of HIV/AIDS	1
Epidemiology of Cancer	1
Health Technology Assessment	1
Immunology	1
Cancer Research	3
Public Health Research	5
HIV/AIDS Research	1
Otros (NSH, EPO, Biobanks, Bioethics)	6
Molecular Pathology	2
Telemedicine	3
Environmental Toxicology	1
Total	46

3

**2015 Human Resources Summons.
Total Granted Contracts per Center**

Center	R+D+I State Plan (*)	Other	Total
CNM	5	5	10
CNE	2		2
CNSA	3		3
ENS	3	1	4
IIER	10	1	11
UFIEC	9	1	10
INVESTEN	2		2
SG	1		1
SGSAFI	1		1
Total	36	8	44

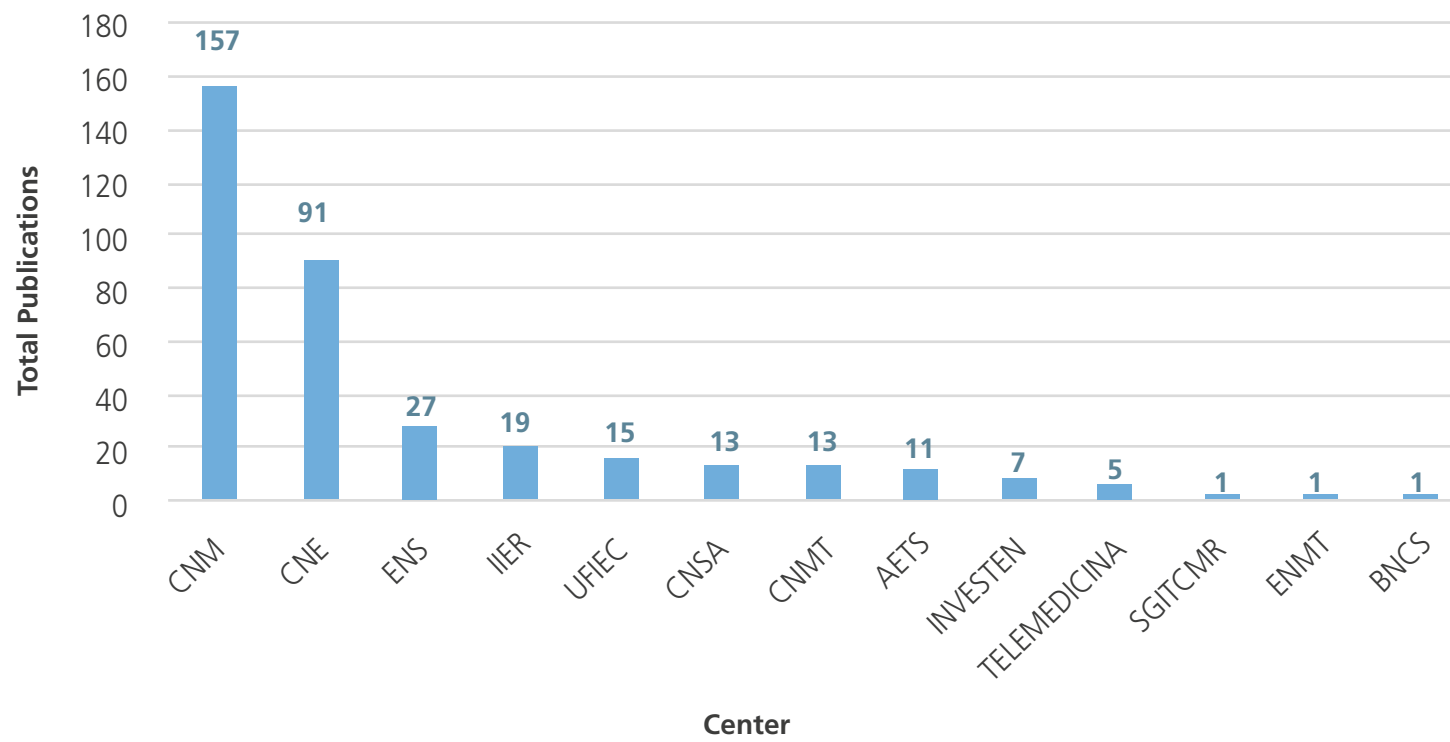
(*) Summons with pending resolutions have been excluded.

2015 Publications and Theses Table

Center	Publications	Theses
AETS	11	1
BNCS	1	-
CNE	91	6
CNM	157	5
CNMT	13	1
CNSA	13	1
ENS	27	3
ENMT	1	
IIER	19	1
INVESTEN	7	1
TCMR-ISCIII	1	
TELEMEDICINA	5	1
UFIEC	15	3
Total	361	23



PUBLICATIONS 2015





4

Training Activities

4 Training Activities

4.1 NATIONAL SCHOOL OF HEALTH

The National School of Health (ENS), funded in 1924, is specialized in postgraduate and continuous training in the Public Health field, Health Administration and Management, International Health, Research Management and other related fields. It develops research, technical studies, consultancy and other services in these areas for different public administrations and scientific, healthcare or development cooperation entities.

Activity Highlights

In response to the International Public Health Emergency created by the recent Ebola virus disease outbreak in Western Africa, the National School of Health, in collaboration with the Brigade of Military Health of the Ministry of Defense and the Alerts and Emergencies Coordinating Center of the Ministry of Health, continued organizing a series of health training workshops and courses for Ebola virus disease in 2015, where NHS professionals of reference hospitals were trained in disease management and in handling personal protective equipment.

The 8-hour workshops had an eminently practical orientation, forming groups of 4-5 students per instructor for practicing the use of Personal Protective Equipment.

They also included a review of the protocol and of the current state of the FSC (EVE in Spanish) and a review of clinical and epidemiological aspects of the disease through an online training platform driven under the ENS Joint Research Institute framework.

In 2015, the ENS prompted a new line of education on ethics and public health, incorporating a course into the MSP program and imparting workshops in the ECDC and in the Netherlands School of Public and Occupational Health Summer School. In addition, within its thematic series, the Public Health Reviews Journal published a collection of articles on Public Health Ethics Training in the European Region edited by the head of this new ENS education area (<http://publichealthreviews.biomedcentral.com/articles/collections>).

Regulated Teaching ENS 2015

	2015	2014	2013	2012	2011
Master's Degree	4	5	6	7	4
Diplomas	2	5	4	6	6
Short Courses	30	49	40	36	48
Class hours	3236	5183	5398	5379	5035
ECTS ¹ Equivalence	130	210	240	239	224
Students	532	1649	553	545	896

(1) ECTS: European Credit Transfer System

Offered Training Courses 2015

Workload (hours)

Master's Degree in Public Health	1000
University Master's Degree in Healthcare Administration	1500
Master's Degree in Management of Health Systems, Technologies and Communications	1500
Master's Degree in Bioinformatics and Computational Biology (2014-2015)	900
Advanced Diploma in Food, Nutrition and Public Health	400
Specialized Diploma in Public Health and Genre	160
Continuous face-to-face training courses	926

Preventive Medicine and Public Health Teaching Unit	2015	2014	2013
Total number of MIR trainee doctors (R1, R2, R3, R4)	7	8	7
Number of students undergoing Master's Degree and Diploma courses	281	221	200
Number of students in continuous training programs	251	1428	353
Total Students	532	1649	553

Scientific Production

During 2015, 4 national and 55 international publications have been produced. Notable among them are:

Belza MJ, Hoyos J, Fernandez-Balbuena S, Diaz A, Bravo MJ, de la Fuente L; Madrid Hiv Rapid Testing Group. Assessment of an outreach street-based HIV rapid testing program as a strategy to promote early diagnosis: a comparison with two surveillance systems in Spain, 2008-2011. *Euro Surveill* 2015 Apr 9; 20(14): pii: 21089. doi: 10.2807/1560-7917.ES2015.20.14.21089 PMID: 25884149

Sordo L, Bravo MJ, Barrio G, Indave BI, Degenhardt L, Pastor-Barriuso R. Potential bias due to outcome-related loss to follow-up in cohort studies on incidence of drug injection: systematic review and meta-analysis. *Addiction* 2015 Aug; 110(8):1247-57. doi:10.1111/add.12940. PMID: 25845977

Bernal-Delgado E, García-Armesto S, Repullo JR. Spain. En: Maresso A, Mladovsky P, Thomson S, et al. Economic crisis, health systems and health in Europe. Country experiences. Copenhagen: WHO; 2015: 487-91. Disponible en: http://www.euro.who.int/__data/assets/pdf_file/0010/279820/Web-economic-crisis-health-systems-and-health-web.pdf

Prieto-Castillo L, Royo-Bordonada MA, Moya-Geromini A. Information search behavior, understanding and use of nutrition labeling by residents of Madrid, Spain. *Public Health*. 2015 Mar; 129(3):226-36. doi:10.1016/j.puhe.2014.12.003. PMID: 25731130

4.2 NATIONAL SCHOOL OF OCCUPATIONAL MEDICINE

The National School of Occupational Medicine (ENMT-ISCIII), is the ISCIII's specialized center for Training, Consultancy and Research in Medicine and Nursing, whose mission is to contribute towards the strengthening of Preventive Systems and the improvement of Health in Workers in concurrence with other National General Administration Agencies, Autonomous Regions and Social Partners. The National School of Occupational Medicine is the National Reference Center of the International Center for Information on Occupational Safety and Health (CIS in Spanish) of the International Labor Organization.

During 2015, the Educational Commission of the ENMT is strengthened, including representatives of national and international key institutions in the Occupational Health field: National Institute of Safety and Health in the workplace (INSHT), National Institute of Social Security (INSS) and the International Training Center of the International Labor Organization, ITC-ILO (CIF-OIT in Spanish).

The ENMT subscribes to 8 new agreements in the field of training, research and implementation of good practice guidelines, with agencies and national associations (National Association of Occupational Physicians in Hospitals, Official College of Doctors and Philosophy and Science Graduates in Madrid, General Workers Union, INSS and the National Institute of Health Management, INSS and the Autonomous Community of Madrid and Castilla La Mancha) as well as international associations (Catholic University of Santa Maria in Peru, Prevecon and the Federation of External Prevention Services).

The following tables summarize the most relevant ENMT information:

Training Courses Offered 2015	Hours	Credits CFC/ECTS
Occupational Medicine Advanced Course 2014 - 2015	800	-
III Scientific Conference on Occupational Health Review Studies	10	-
Introduction to Dermoscopy for Occupational Doctors	7	0.9 CFC
Introduction to Systematic Reviews	30	3.5CFC
Introduction to Pneumoconiosis in the Workplace	25	4,3CFC
Occupational Diseases for Primary Care Doctors	40	6,9CFC
Occupational Medicine Advanced Course 2015-2016	800	-
Diploma in Assessment on Labor Disability and Body Damage (Miguel Hernandez University)	350	35 ECTS
National Conference on Education and Professional Development of Occupational Nursing	4.5	-
Medical Disability Assessment Diploma (Ibermutuamur agreement)	350	-
Functional Tests Update	40	4,2CFC
University Expert in Occupational Diseases	200	20 ECTS
Vaccination in the Workplace	40	5,5 CFC
Indoor Air Quality	25	4,6 CFC

Global Indicators- Training	2010	2011	2012	2013	2014	2015
Total number of MIR in training (R1, R2, R3, R4)	155	165	160	149	138	127
Number of students in continuous face-to-face training	242	476	682	509	406	166
Number of students undergoing online training	150	308	494	236	390	347
Number of students in continuous training through educational agreements	170	215	197	53	62	22
Total class hours taught	3.101	4.211	3.613	3.729	2.072	1.921,5

Global Indicators- Research, Scientific Activity and Scientific dissemination

Activity	2010	2011	2012	2013	2014	2015
Research projects associated to educational programs	48	52	69	83	75	57
Publications in scientific journals	15	14	12	9	10	9
Communications/ Presentations	19	23	19	11	21	15
Original Articles Journal of Occupational Medicina and Safety in the Workplace Journal	30	36	35	32	58	41



5 Internationalization

Through the Strategic Action in Health, the Institute of Health Carlos III is involved in coordinating capabilities and funding programs for R+D+i between European countries and regions (ERA-Nets and ERA-Nets cofund), in joint programs under Article 185 of the European Unions Functioning Treaty (TFUE), in the Joint Programming Initiative (JPIs), and in the preparation of European Joint Programs (EJPs: Human Bio monitoring y zoonosis / Med Vet one health) as well as being the National Contact Point for the III EU 2014-2020 Health Program.

The ISCIII coordinates EULAC Health, which has produced a roadmap to strengthen health research cooperation between EU countries and the CELAC (Community of Latin American States and the Caribbean), has presented JIRI-Health (Joint Initiative on Health Research and Innovation) in Brussels on June 2, provides scientific support to the SOM (Senior Officers' Meetings) Health Work Group created by the UE-CELAC Summit in Madrid (2010) and has provided topics for ERANET LAC health summons. ISCIII has also participated in producing a roadmap in personalized medicine (IC PerMed) that finalized in 2015, and that serves as the basis for a comprehensive European global action in preparation for 2016.

In addition, the ISCIII participated in two global research consortia: IRDiRC (International Rare Diseases Research Consortium) and GloPID-R (Global Research Collaboration for Infectious Disease Preparedness, for providing an effective 48 hour response to a significant outbreak of a new infectious or re-emerging disease with pandemic potential).

The ISCIII represents Spain and covers its contribution to IARC (International Agency for Research on Cancer, of the OMS) and three European research infrastructures (ECRIN-ERIC, European platform for clinical trials, EATRIS-ERIC, Translational Medicine, and ELIXIR, -omics data). Similarly, it works on three other infrastructures in preparation included in the ESFRI roadmap (ERINHA, BSL-4: biological safety laboratories for high community risk pathogens type 4, Eurobioimaging, digitization of medical imaging and biological microscopy, and EU-Openscreen, screening of molecules for therapeutic activity, a sustainable European infrastructure for Chemical Biology, supporting life science research and its translation to medicine, agriculture, bio industries and society).

The ISCIII holds the position as President of AAL and of the Assembly of the countries members of the ECRIN-ERIC through the General Sub direction of International Programs for Research and Related Institutions, and participates in the ESFRI Health & Food Strategic Working Group.

Promotion and Participation in the Research and Innovation Framework Program Horizon 2020

Last year 2015 has been a period in which the awareness, promotion and dissemination of the H2020 program, and the existing opportunities for the area of health and science has been intensively pursued. The activity during this period has focused on promoting, training and assisting in the preparation of proposals. The ISCIII Office of European Projects has organized 21 courses or workshops, cooperating in 22 other training actions. Likewise, 23 information days on open calls have been organized and another 43 meetings were organized by other organizations and distributed in 13 autonomous communities. To these days, it is convenient to add the details of the launching of ten newsletters, as well as the renewal of the web portal <http://www.eu-isciii.es>

In the area of health, the results of the Spanish participation in 2015 have continued on the good path of 2014, both in terms of participation and success, as well as leadership. Thus, Spain has 43 cumulative projects for 2014 and 2015, of the 322 projects financed in total, being the second country in coordinated projects (13.35%), only behind the United Kingdom and ahead of Germany or the Netherlands. Translated this leadership to subsidies obtained, it should be noted that Spain is obtaining an average annual funding from the start of H2020 above 45 million euros for these two years. This represents a return of more than 8% on EU funding. This milestone puts Spain in fifth place in the health sector, behind only the UK (18.61%), Germany (15.28), the Netherlands (13% , 60%) and France (10.62%). On this rate of return, we must highlight the traction effect of the ISCIII environment plus the National Health System, which represents 42% of the successful participations and 45% of the returns (EU 28).

The ISCIII has consolidated its position in 2015 in terms of projects and increased by about 15% the funding received under H2020 compared to FP7, surpassing the threshold of two million euros again. In addition, it should be noted that in 2015, 31 proposals were submitted to H2020, with 10 of them being financed, representing an approximate success rate of 33%, well above the H2020 health program rates, closer to 10%

Coordination and alignment of R+D+i (I+D+i in Spanish) national programs and their funding

During 2015, the ISCIII has participated in 5 ERA-Nets (NEURON-II, ERASysApp, EuroNanoMed-II, Infect-ERA, ERANET LAC); 4 ERA-Nets cofund (E-RARE-3, TRANSCAN-2, ERACoSysMed, y JPco-fuND); 4 JPIs (JPND, JPI AMR, JPI HDHL y JPI MYBL); 2 joint programs under co-decision of the European Parliament and Council (EDCTP-2 y AAL-2), as well as in 10 transnational joint summons within the framework of these initiatives, through which 30 Spanish scientific research groups have been funded with a total sum of 2,618,117 € under “additional cost” (representing a 53% increase compared to 2014).

ERA-Net

Objective: coordination of R+D+i programs and funding between European countries and regions. One of its greatest achievements has been the launching of joint summons for translational research projects whose procedures are of common ground and consensuated between all participating agencies. During 2015 the ISCIII has participated and/or financed the following ERA-Net:

- NEURON II (Neuroscience 2012-2015). 23 funding bodies and 2 research bodies from 14 countries participate. In 2015 2 parallel project summons were launched in which the ISCIII participated, financing 4 Research Groups in Spain with 60,000€.
- ERASysAPP (Biology Systems). Has launched two transnational summonses for research that have financed 7 research projects. The ISCIII has managed the call office/joint call Secretariat.
- EuroNanoMed-II (European network for transnational collaborative RTD projects in the field of Nano medicine). 20 funding bodies from 16 countries participate. The 2015 summon, of nearly 10 M€, has funded 11 projects. The ISCIII has funded 4 scientific groups based in Spain with nearly 0.5 M€.
- Infect-ERA (Human Infectious Diseases). 14 funding bodies from 12 countries participate. The ISCIII has participated in the 2015 summon with an initial commitment of 250,000€, funding one scientific group in Spain.
- ERANET-LAC (Cooperation with Latin America and the Caribbean). 18 funding bodies from 8 European Countries and 8 from the CELAC participate. In the 2014/2015 summon, whose Call Office/Joint Call Secretariat has been managed by CYTED, 14 translational projects in health have been funded with 10.4M€, in which the ISCIII has funded 7 research groups in Spain with 606,549€.
- E-RARE-3 (on Rare Diseases) 26 funding bodies from 17 countries participate. In the 2015 cofund summon of 20 M€, 19 transnational projects have been funded in which the ISCIII has funded 4 groups with 339.718,4€.

- TRANSCAN-2 (Translational Cancer Research). 28 funding bodies from 19 countries, including two Spanish funding agencies: ISCIII y FICYT participate. In 2015, 16 projects were funded with 17.2 M€. The ISCIII has funded 6 scientific groups based in Spain with 696,753€.
- ERACoSysMed (Collaboration on Systems Medicine). 15 funding bodies from 14 countries participate. In 2015 the first summon was launched with 12 M€; the ISCIII has managed part of the Call Office/Joint Call Secretariat and has funded 3 scientific groups from Spain with 297,000€.
- JPco-fuND (Establishing synergies between the JPND Research and H2020). In the 2015 cofund summon, of 35 M€, the ISCIII financed one scientific group based in Spain with an initial commitment of 0.5 M€.

Joint Programming (Joint Programming Initiatives –JPI’s)

Objective: strengthen the coordination and integration of Member States research programs to address common problems, avoid duplication and promote excellence in research. In 2015, the ISCIII has participated in the following JPIs as a funding agency:

- JPND (Alzheimer and Neurodegenerative Diseases). 28 countries participate and the ISCIII collaborates in the implementation plan of the JPNDs Strategic Research Agenda.
- JPI AMR (on Antimicrobial Resistance). 22 countries participate. The objective is to address the growing problem of antimicrobial resistance through a common strategic agenda. It is foreseen that an annual summon will be launched for transnational research projects starting in 2016.
- JPI HDHL (A Healthy Diet for a Healthy Life). The objective is to coordinate investigation on the impact of diet and lifestyle on health in the 25 participating countries. The ISCIII participates both in this JPI as well as in support initiatives and implementation (CSA and ERA-Net cofund ERA-HDHL, initiated December 2015, for cofunding projects on nutrition and health Biomarkers).
- JPI MYBL (More Years, Better Lives-The Potential and Challenges of Demographic Change). 15 countries participate. In the 2015 projects joint summon (Extended Working Life and its Interaction with Health, Wellbeing and beyond) the ISCIII led the preparation of documents and formats for the summon.
- JPsustaiND (Neurodegenerative Diseases). CSA for sustainability and globalization of JPND. The ISCIII co-leads the development and implementation of a structure for sustainability of JPND, the extent of their capabilities and alignment of National Research Programs in Neurodegeneration.

Article 185 Initiatives of the Treaty on the Functioning of the EU

Objective: integrate research efforts of participating Member States in the definition and funding of a joint research program for the EU.

- AAL-2 (Active and Assisted Living). 2014-2020 Joint Research Program for funding research applied towards improving the lives of the elderly and strengthening the European industrial fabric, through the demand for new products, systems and/or services based on Information Technology and Communication services. Funding for the annual AAL Forum and other support measures. The ISCIII has participated in the 2015 summit (Living active and independently at home) with an initial commitment of 200,000€.
- EDCTP-2 (European & Developing Countries Clinical Trials Partnership). 2014-2020 Joint Research Program for funding clinical trials between European and African Sub-Saharan countries and capabilities for them in this region of the world. It has expanded its thematic spectrum to neglected diseases and the EU co-funding has grown from 200 M€ to 680 M€. ISCIII's current commitment is of 200,000€ per year.

Other activities of international coverage

During 2015 technical support and counsel has been provided to the General Department of International Relations of the MSSSI to establish the position to be adopted by Spain in the OMS Secretariat Report (EB 136/30) which seeks the creation of international funding mechanisms to promote and provide sustainability to the R+D+i on Type III diseases and the specific needs of poor countries for Type I diseases. Within this range, counsel has been provided in regards to the position to be adopted at the next evaluation of the Global Strategy Plan of Action on Public Health, Innovation and Intellectual property.

The ISCIII maintains strong leadership and responsibility with the Ibero-American Ministerial Network for Learning and Health Research (RIMAIIS). In 2015 5 major studies were performed and are being evaluated for publication in the American Journal of Public Health: Bioethics Research in Ibero-America; Case studies on good practice policies based on scientific evidence; State of Art on Education for Health Research in the Region; Proposal of Indicators for the Evaluation of Science and Technology in Health in Ibero-America, and lastly, an Update Report on Policies and Programs of the National Research System at Ibero-American level.

The ISCIII belongs to the governing boards of the WHO (OMS in Spanish) Special Program for Research in Tropical Diseases and to the International Association of the Public Health Institute. At a national level, coordination has been strengthened with the General Secretariat of International Coordination for the Development of MAEC and with the AECID, with a view towards harmonizing policies in the R+D+i for health.



6 Regulations, Ethics

6 Regulations, Ethics

6.1 GUARANTEES COMMISSION FOR THE DONATION AND USE OF HUMAN CELLS AND TISSUES AND NATIONAL REGISTER OF RESEARCH PROJECTS, NATIONAL REGISTER OF BIOBANKS, BIOETHICS COMMITTEE.

6.1.1 Guarantees commission for the Donation and Use of Human Cells and Tissues

Guarantees Commission for the Donation and Use of Human Cells and Tissues and National Register of research projects that involve the use of human embryonic origin cells or tissues.

Law 14/2007, of July 3rd, on Biomedical Research created the Guarantees Commission for the Donation and Use of Human Cells and Tissues, as a collegial body, attached to the Institute of Health Carlos III, with a permanent and consultative nature, aimed towards counseling and orienting research and experimentation with human embryonic biological samples, and contributing to the update and dissemination of scientific and technical knowledge in this field.

During 2015, five Commission meetings have been celebrated; where a total of 51 research projects have been informed.

6.1.2 National Register of Bio banks

The National Register of Bio banks, created by the Law of Biomedical Research and developed by Royal Decree 1716/2011, on November 18th, which establishes the basic requirements for authorization and operation of bio banks for medical research and treatment of biological samples of human origin, and regulates the operation and organization of the National Registry of Bio banks for Biomedical Research. Log activity initiated in 2012 continues during 2015, having proceeded to register 183 collections and 1 bio bank.

6.1.3 El 6.1.3 Spanish Bioethics Committee

The Spanish Bioethics Committee, created by the Law 14/2007, on July 3rd on Biomedical Research, is constituted as a collegial body, with an independent and consultative nature, for related ethical and social implications of Biomedicine and Health Sciences.

6.1.3.1 Main activities performed by the Spanish Bioethics Committee during 2015:

The committee's participation in the following national and international events: III Bioethics Congress: "Ethical Aspects of Accessing Health Data", organized by the Institute of Health Carlos III's Ethics Committee for Research and Animal Welfare, celebrated Madrid on November 19th and 20th.

6.1.3.2 Elaborated Documents:

Spanish Bioethics Committee report on prenatal genetic counseling.

6.1.4 Activity of the ISCIII Ethics Committee for Research and Animal Welfare (CElyBA)

Evaluation Activities

Informed projects: During 2015, 91 research projects with humans and 65 animal procedures from both ISCIII centers and Foundations, as well as other external centers to the ISCIII have been evaluated, representing a total of 156 projects.

Training and dissemination activities. Organization and execution of the III Bioethics Congress: "Ethical Aspects of Accessing Health Data", on November 19th and 20th in the ISCIII's Ernest Lluch Auditorium.

6.2 QUALITY UNIT

The Quality and Planning Unit develops a cross-methodological role, providing support and counsel to other ISCIII structures.

The following actions have been developed in 2015:

Design and implementation of the Improvement Plan for Management of Aids of the Strategic Action in Health (AES). The design of the plan, whose aim is to establish a process management system, has led to the development of an AES Process Manual that globally describes the management procedure of the AES and the processes for its development. It shows the interrelationship between processes and the various stages of each of them, coordinating the activities in different ISCIII areas that intervene. Subsequently, for each process, all relevant aspects that are necessary for guaranteeing their quality have been identified



and prioritized, and evaluation indicators have been designed. A monitoring system has been established to check on the correct development of the summons periodically, according to the previously established quality standards, based on compliance with current legislation and the good practice criteria acquired by professionals through their experience.

Collection and validation of ISAM sheets of the entire ISCIII (in compliance with RD 951/2005, which establishes the General Framework for Quality Improvement in the AGE). The ISAM sheets gather information for the “Annual Report of Ministerial Activity in relation to Programs within the General Framework for Quality Improvement in the General State Administration.”

