



2017

Annual Report



ehugroup 

Achucarro
BASQUE CENTER FOR NEUROSCIENCE

scientia ad remedium

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FOREWORD

Dear reader,

Welcome to the Annual Report of **Achucarro Basque Center for Neuroscience**. At the end of 2017, we completed our first strategic period (2014-2017), a time that has been crucial for the consolidation of our organisation as a Basque Excellent Research Centre (BERC) and as an international reference in the field of glia research.

In this four-year period we published over 170 research papers in indexed international journals, the vast majority of which were ranked in the first quartile of their research area, and over a third in the first decile. Moreover, four out five of our articles reflect the very active collaborations with international partners in top research centres over the world. Overall, this scientific production received more than 3.000 cites, an average of 18 cites per paper.

An important milestone of past year was the inauguration in June of our new headquarters within the Science Park of the UPV/EHU in the campus of Leioa



This new location has the space and facilities required to continue our development and growth. Importantly, this strategic localization facilitates a fruitful interaction with the biomedical community in the university campus of Leioa and also the recruitment of talented graduate and undergraduate students.

In 2017 we also underwent a process of assessment and review of the activities and achievements of our centre during 2014-2017, with the objective of reflecting on the challenges for the future and the next strategic period, 2018-2021. During this process we had an on-site visit by our International Scientific Advisory Committee (ISAC) which carried out the evaluation of the ongoing scientific projects and future plans of the research groups. This in-depth review helped us to implement new ideas to further develop the cohesiveness of our organisation and to increase our international visibility.

I invite you to carefully read this Annual Report that contains more detailed and precise information about all the activities and milestones of 2017.

Carlos Matute
Scientific Director

We strive to be a holistically excellent organisation. This means that our management and operation, and the outcome of them meet high quality standards. The overall aim of our management processes is to effectively and efficiently implement our strategy and operations.

*To deploy the strategic objectives set by our Board of Trustees, we designed and continuously develop a management model based on processes, following the guidelines and recommendations of the **European Foundation for Quality Management (EFQM)** and the **Basque Foundation for Quality (Euskalit)**.*

1. STRATEGY AND MANAGEMENT

In 2012 the Basque Government fostered the creation of the Basque Research Centre in Neuroscience within the network of Basque Excellence Research Centres (BERC). The founding partners of this new centre are Ikerbasque - the Basque Foundation for Science, the University of the Basque Country (UPV/EHU), and BIOEF – the Basque Foundation for Health Innovation and Research, which currently compose the Board of Trustees of the legal entity behind the centre, a non-profit foundation, under the Basque and Spanish laws.

In the 2017 year we have completed our 2014-2017 strategic period, aligned with the periods of the BERC programme calls funded by the Basque Government.

Scientific Plan 2014–2017

The main strategic objective of ACHUCARRO is to contribute to the development of a socially and economically sustainable society. To do this we strive to develop world-class research in the study of neuron-glia biology in the normal and pathological brain. Being aware that this task is huge and will take generations, our will is also to contribute to the training of future neuroscientists and to advocate about the importance of the advance of brain knowledge.

The leverages that will support this endeavour are well known in our region and worldwide:

- ▶ Recruit, Reintegrate and Retain **talented research personnel**, to perform excellent research and contribute to the **advanced post-graduate training**.
- ▶ Incorporate and maintain **modern infrastructures**, in our brand-new headquarters, close to the University (to foster academic and research synergies); and incorporating the latest **technologies and equipment** to let the centre operate in the frontier of knowledge.
- ▶ Perform **state-of-the-art research** centred in glial cells, to contribute to the discovery of **new therapies** for neurological diseases for the benefit and **well-being of the Society**.

To meet these goals, ACHUCARRO designed a Strategic Plan for the period 2014–2017 that contains **three high-level research programmes** including different areas that involve the coordinated and complementary expertise of the different research groups from the centre.

- ▶ **Characterization of the role of glial cells in the physiology of the nervous system**
 - roles of astrocytes in synaptic communication
 - neurotransmitter signalling during neurogenesis and gliogenesis
 - mechanisms of microglia phagocytosis during neurogenesis
- ▶ **Characterization of structural and functional changes of neuronal–glial networking in the aged brain**
 - age-dependent remodelling of neuronal–glial signalling
 - regulation of the intrinsic properties of neural stem cells in the adult hippocampus
- ▶ **The role of neuroglia in neurodegenerative diseases and other neurological disorders**
 - research on general mechanisms of neuron and glial cell death
 - understanding the pathophysiology of Alzheimer's disease and epilepsy
 - autoimmune pathogenesis of multiple sclerosis (MS) and neuroinflammation



Carlos Matute (Scientific Director), Iñigo Urkullu (Lehendakari, President of the Basque Country), Emma Jiménez (niece-in-law of Achúcarro) and Nekane Balluerka (Rector of the UPV/EHU) at the inauguration event of the new headquarters (June 2017)

Management Plan 2017

There have been two main management challenges this year: the process of reflection to design our strategy for the next four years, and the moving of our premises to a new location.

We faced 2017 as a year of changes and redefinition. We expected (and successfully developed) the assessment visit of our International Scientific Advisory Committee (ISAC) in June, and the preparation of the next BERC application for the last quarter of the year.

When looking at the main output indicators set by the Basque Government, we realised the huge effort done in the 2014-2017 period to deploy the strategic plan and the research programme we defined 5 years ago.

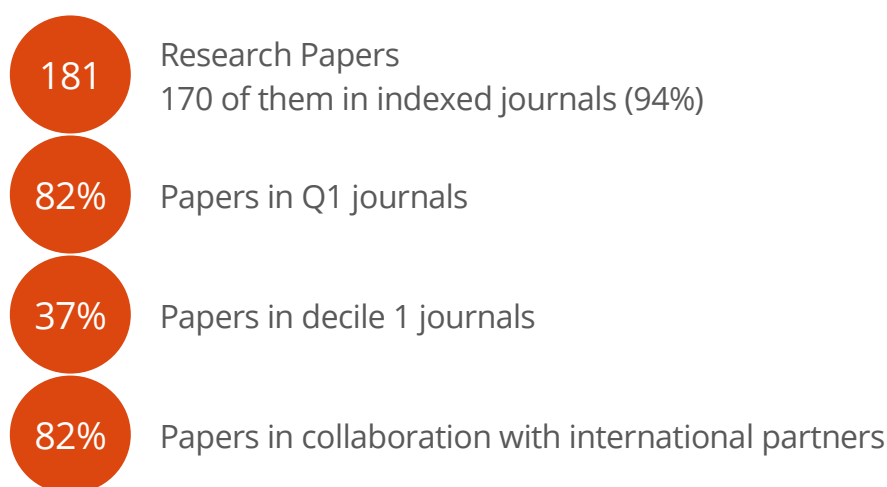


Figure 1. Main output indicators of the 2014-2017 period

Consequently the conclusion of the strategic reflection processes suggested to continue and reinforce the main strategic pillars based on the attraction of talent, incorporation of state-of-the-art technologies and infrastructure, and the maintenance of the guidelines of the research programme.

The moving of our premises from the initial establishment headquarters in the Science and Technology Park in Zamudio, to the Sede Building within the Science Park of the UPV/EHU in Leioa required us to redefine many organisational aspects. Although the distance from both locations is only 15 kilometres, the supervision of the completion of the works, the preparation of the move, the move itself and the new operation standards in Leioa have required extra work and dedication from all of us. It all deserved all our efforts, because for the first time in the short life of ACHUCARRO, most of the research groups and infrastructure are sharing the same location, which brings an overall efficiency gain to our organisation.

This location and environment change induced changes in our organisation and management processes, mainly in the support processes that evolved to adapt to the new reality.

Moving from a distributed organisation, to a unified one, with core central research facilities, required hiring of a designated Facility Manager, in charge of the management of these resources. Therefore, with the addition of this person, we improved, updated and distributed the responsibilities other the Support Processes.

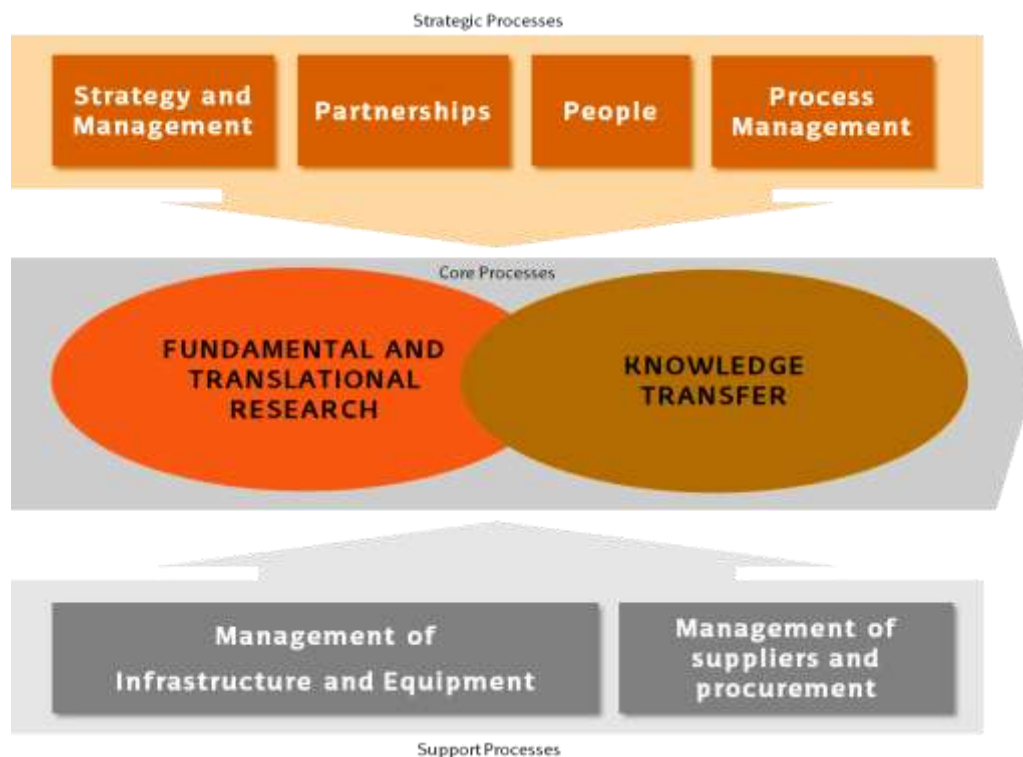


Figure 2. Map of Management Processes

Transparency and Accountability

ACHUCARRO has been a pioneer within the BERC centres in terms of publishing our Annual Reports, Accounts and Audit reports since 2012, being ahead of the legal requirements.

Currently, the requirements of the social context for openness, accountability, ethic attitudes and communication to and with the Society are becoming a legal requirement and social claim for the organisations that management of public funding.

For us, the principles and activities towards openness and transparency are the foundations to strengthen the sustainability of our project, so we keep an updated section on our website to communicate about these subjects.

<https://www.achucarro.org/transparency-and-sustainability>

This document is also a reflection of this commitment.

Due to the commitment of the Direction of the centre, ACHUCARRO is the first non-academic research organisation in the Basque Country to reflect and develop an Equality Plan.

Equality Plan 2018-2021

Another milestone for ACHUCARRO has been to develop an Equality Plan. With the support of Emakunde, the Basque Institute for Women and the methodologies they propose for this kind of initiatives, we underwent an internal analysis and reflection process to improve the policies and our organisational culture towards the Equality.

Since the methodology and framework we used is closely linked to gender equalities, some of the main actions and activities in our Plan for the next 4 years are also related to that, but our scope is wider, and strive to cover all kind of potential inequalities.

The 100% of the personnel participated in, at least one of the dynamics, surveys or working groups created to attain this Plan. The process, carried out from June to November was structured in three stages: an initial analysis or diagnose stage, before the design stage, to conclude with a training and dissemination stage.

This first plan identifies four main objectives or areas of improvement:

1. Promoting equal opportunities in positions of responsibility
2. Generate working environments and conditions that facilitate the co-responsible conciliation of personal, family and professional life
3. Incorporate the gender perspective in the policies, products and operating dynamics
4. Promote inclusive leadership styles

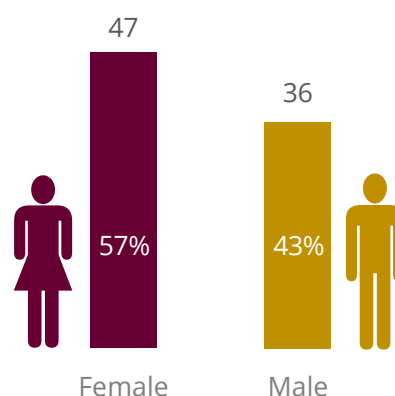


Figure 3. Current gender ratio

Partnering and sharing efforts with other individuals and institutions is crucial for achieving our more ambitious objectives.

The importance that we confer to institutional relationships required a process to properly manage and maintain mutually beneficial partnerships. This process classifies the different types of collaborations, attending to the framework environment or the impact of each partnership in the development and achievement of our strategic objectives.

2. PARTNERSHIPS AND COLLABORATIONS

According to the objectives and fields of activity, we classify the collaboration and partnership relationships we create and maintain in three different types: Institutional, Strategic, or Operational.

Institutional Alliances

Institutional partnerships and collaborations are based on a partnership agreement or similar document that enables us to maintain a close collaborative relationship in specific areas. To some extent, such alliances are also strategic in nature, as indicated by the agreements signed with Ikerbasque and the UPV/EHU for the appointment of personnel.

We currently hold institutional agreements with:

Basque Government

- ▶ Agreement to support the activities of the centre in the period 2014–2017

Ikerbasque

- ▶ Framework Agreement for the appointment of research staff: Ikerbasque Research Professors and Ikerbasque Research Fellows
- ▶ Specific agreements and annual protocols for the co-funding of Ikerbasque research staff: Research Professors and Research Fellows

University of the Basque Country (UPV/EHU)

- ▶ Framework Collaboration Agreement
- ▶ Specific agreement for the appointment of the Scientific Director
- ▶ Specific agreement for the appointment of teaching and research and personnel
- ▶ Specific agreement for the appointment of academic and research collaborators
- ▶ Specific agreement to manage the application to European projects

Basque Science, Technology, and Innovation Network

- ▶ Attachment to this network and recognition as a BERC (Basque Excellence Research Centre).

Strategic Alliances

We consider strategic alliances to be those that we establish with all kinds of institutions operating in our area, either generally or specifically. Apart from partnerships that we systematically develop with the members of our Board of Trustees, our Strategic collaborators are the following:



European Commission – HRS4R Community

Following our endorsement of the European Charter for Researchers fostered by the European Commission, we were invited to participate in a work group with institutions involved and committed to the same principles and policies. This forum provides us with valuable access to the most current policies of the Directorate General for Research and Innovation and other European research institutions.



Euro-BioImaging

The joint effort of ACHUCARRO and the Institute of Biophysics (a joint research institution created by the Spanish National Research Council – CSIC – and the University of the Basque Country) to run a node candidate within the Euro-BioImaging (EuBI) network has continued developing this year. EuBI has started operating in interim mode.



Bizkaia Talent

Established in 2005 with the support of the Provincial Council of Bizkaia, Bizkaia Talent is a non-profit organization that fosters and facilitates the attraction, connection, and retention of highly qualified professionals to the Basque Historic Territory of Bizkaia. Bizkaia Talent is a strategic partner and an ally of ACHUCARRO, which takes our name and objectives to the many international scientific events they attend, supporting our talent attraction process.



Euskampus

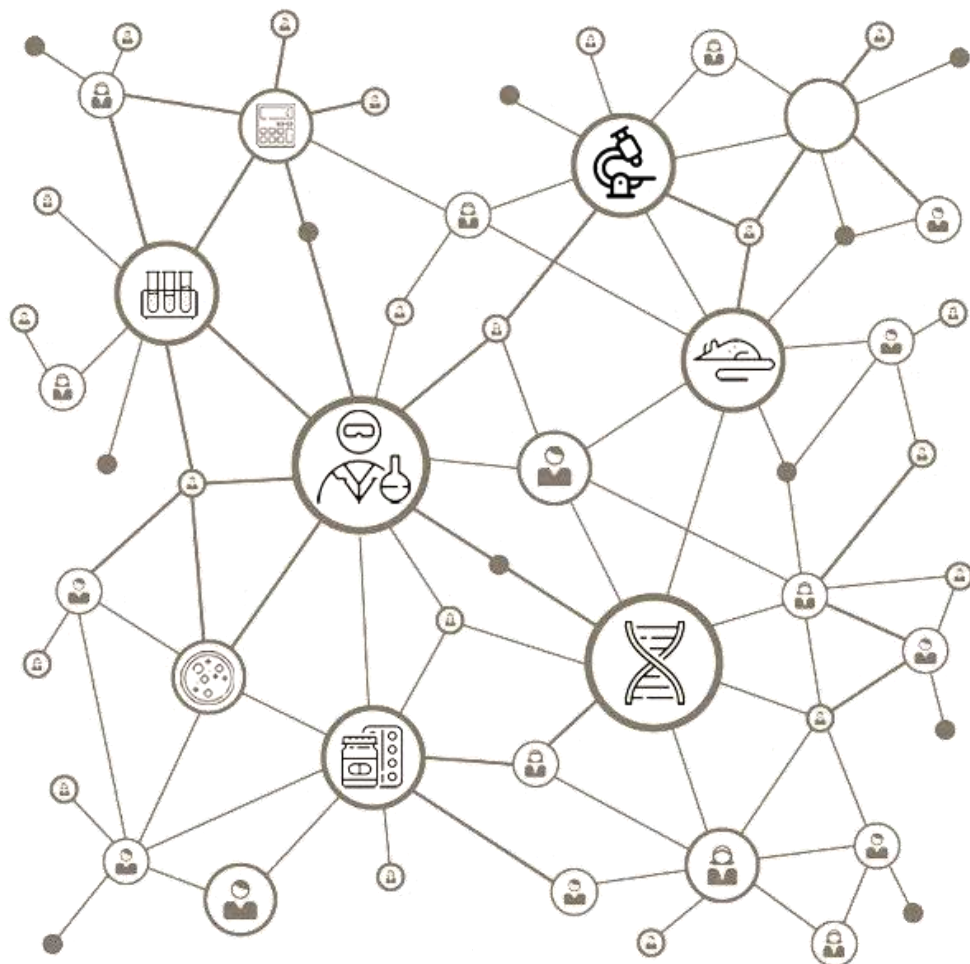
The Foundation created by the UPV/EHU, DIPIC and Tecnalia to develop the International Campus of Excellence has built a solid link with the University of Bordeaux, to consolidate cross-border collaborations in the Aquitaine – Basque Country euro-region. This environment is a reference for us, due to the huge potential of collaboration with the *Bordeaux Neurocampus*.

Operational Alliances and Partners

Over the last 6 years we have signed agreements with many research organisations within the Basque Country and Spain when we have jointly identified collaboration areas and projects.

ACHUCARRO collaborates with other BERC centres like **BC3** (Climate Change), **BCAM** (Applied Mathematics, Computational Neuroscience), **BCBL** (Cognition and Language) and the **Institute of Biophysics** (Biophysics, Imaging capabilities); with **BioCruces** - Health Research Institute (Translational Neuroscience); and with two of the Cooperative Research Centres (CIC) **biomaGUNE** (Imaging) and **nanoGUNE** (nanoscience).

In terms of infrastructure and services, we highlight the **Bizkaia Science and Technology Park**, a public company of the Basque Government and own and manages the network of innovation environments and locations in the Basque Country, which provides us the basic infrastructure for establishing our premises, and is a loyal partner for many ideas and projects we launch. **i2Basque** is the Basque Academic Network provides telecommunication and ICT support services and infrastructure to the member organizations of the Basque Science, Technology, and Innovation Network.



The International Scientific Advisory Committee is the main strategic advisory body of ACHUCARRO. Its primary role is to advise, supervise, and assess the objectives and performance of the different groups and professionals of the centre.

International Scientific Advisory Committee (ISAC)

The BERC centres are required to have an ISAC, and to subject their results and future objectives to their opinion and advise.

Our ISAC consists of distinguished colleagues that provide us with their view on the different fields and expertise areas covered by the Research Programme of the centre.



Figure 4. Members of the ISAC in 2017

Following our schedule of meetings and assessment protocols, in June 2017 we held the second plenary meeting of this Committee, where they evaluated and assessed our 2014-2017 performance, and the plans for 2018-2021.

The ISAC spent two full days attending the presentations of all the Group Leaders, reviewing the ongoing projects and preliminary results, and discussing with the younger members of ACHUCARRO.

All the process was very enriching for all the parties, and the final outcome was an Assessment Report that was sent to the Board of Trustees and the representatives of the Basque Government for their supervision and evaluation.

The overall opinion expressed by the ISAC in their report was excellent:

"The committee's unanimous general opinion was that the centre is timely and should be strongly supported. It is still at an early stage of development and consequently is potentially vulnerable to interruption of adequate financial and administrative support.

The overall trajectory of the centre is highly appropriate in regard to its scientific goals and we are convinced that the centre is fast becoming one of the premier scientific groups in the world focused on understanding the functions and dysfunctions of glial cells through basic science investigation.

The conditions for robust scientific success are all in place: the directions of the research are appropriately diverse and sufficiently rigorous, the scientific infrastructure is thoroughly modern and exceptionally well organized and the resident scientists are highly creative and very enthusiastic.

Important discoveries are certain to result."



One of the working sessions of the ISAC

ACHUCARRO is a research organisation, a knowledge creation and knowledge transfer organisation. Currently, humans, talented people are the individuals that can optimally do that work. This is why we prefer to talk about people, and not human resources.

3. PEOPLE

At the end of 2017, ACHUCARRO was an organisation of 83 people.

According to our objective for efficient operations and management, we keep a management team of 4 people, 4 Laboratory and Facility technicians, and 75 researchers on the different stages of the research career.

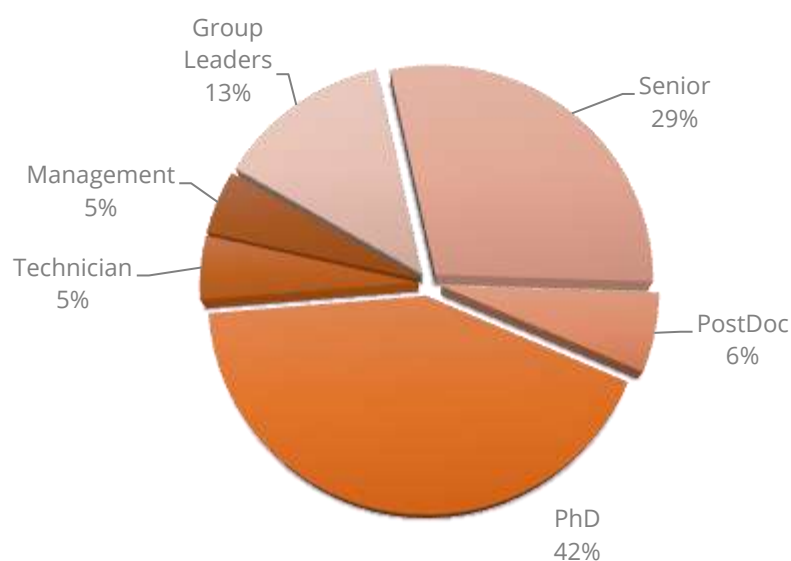


Figure 5. Ratio of personnel per function / position

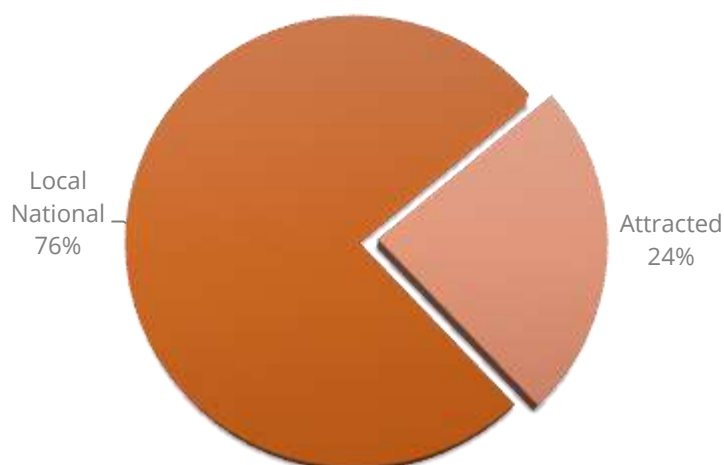


Figure 6. Ratio of people attracted talent vs local or national

Open, Transparent, Merit-based Recruitment

The Board of Trustees and the Direction of ACHUCARRO endorsed the **European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers** fostered by the European Commission. In fact, this was the first decision to be approved right after the establishment of the centre.

This led to a process of internal analysis and the corresponding definition of policies to strategically manage the attraction, development and retention of talented professionals.

In September 2013, the European Commission awarded us with the HR **Excellence in Research** recognition to our commitment with the *European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers*, and the rest of the recommendations (OTM-R) set by the Human Resources Strategy for Research (HRS4R) working group.



<https://www.achucarro.org/hrs4r>

Research Assessment

Complementary to the policies and recommendations, we build on an assessment and evaluation process that do not merely rely on journal impact factors. We apply the policies that we would like others would apply to us.

When assessing research professional profiles, our Selection Committee follows the principles of the **San Francisco Declaration on Research Assessment (DORA)**.



The Declaration on Research Assessment recognizes the need to improve the ways in which the outputs of scholarly research are evaluated. It is a worldwide initiative covering all scholarly disciplines and all key stakeholders including funders, publishers, professional societies, institutions, and researchers.

Appointed Staff (2017/12)

Svein **Achicallende** (*PhD Student*) Elena **Alberdi** (*Senior Researcher*) Iraide **Alloza** (*Senior Researcher*) Jimena **Baleriola** (*Group Leader*) Sol **Beccari** (*PhD Student*) Itziar **Bonilla** (*PhD Student*) Miren Josune **Canduela** (*Senior Researcher*) Estibaliz **Capetillo** (*Senior Researcher*) Fabio **Cavaliere** (*Senior Researcher*) Juan Carlos **Chara** (*Technician*) Joanna **Danielewicz** (*Postdoctoral Fellow*) Irune **Díaz** (*PhD Student*) María **Domercq** (*Senior Researcher*) Irene **Durá** (*PhD Student*) Jon **Egaña** (*PhD Student*) Izaskun **Elezgarai** (*Senior Researcher*) Juan Manuel **Encinas** (*Group Leader*) Laura **Escobar** (*Technician*) Marian **Fernández** (*Management Assistant*) Laura **García** (*Project Manager*) Fernando **García-Moreno** (*Senior Researcher*) Inma **Gerrikagoitia** (*Senior Researcher*) Paula **Giménez** (*PhD Student*) Sonia **Gómez** (*Senior Researcher*) Pedro **Grandes** (*Group Leader*) Mazahir T. **Hasan** (*Group Leader*) Francisco **Llaveró** (*Postdoctoral Fellow*) Celia **Luchena** (*PhD Student*) Miriam **Luque** (*PhD Student*) Artur **Luzgin** (*PhD Student*) Andrea **Manterola** (*PhD Student*) Saioa **Marcos** (*Technician*) Soraya **Martín** (*PhD Student*) Ainara **Martínez** (*Technician*) Luis **Martínez Millán** (*Senior Researcher*) Susana **Mato** (*Senior Researcher*) Carlos **Matute** (*Group Leader and Scientific Director*) Aitor **Medrano** (*PhD Student*) Jorge **Mena** (*PhD Student*) Juan **Mendizabal** (*Senior Researcher*) Alejandro **Montilla** (*PhD Student*) Carolina **Ortiz** (*PhD Student*) Ana **Palma** (*PhD Student*) Aitor **Palomino** (*Facility Manager*) Iñaki **Paris** (*PhD Student*) Oier **Pastor** (*PhD Student*) Sara **Peñasco** (*PhD Student*) Fernando **Pérez-Cerdá** (*Senior Researcher*) Alberto **Pérez-Samartín** (*Senior Researcher*) José Ramón **Pineda** (*Senior Researcher*) Ainhoa **Plaza** (*Postdoctoral Fellow*) Nagore **Puente** (*Senior Researcher*) Tania **Quintela** (*Postdoctoral Fellow*) Almudena **Ramos** (*Senior Researcher*) Paula **Ramos** (*PhD Student*) Leire **Reguero** (*Senior Researcher*) Irantzu **Rico** (*Postdoctoral Fellow*) José Julio **Rodríguez Arellano** (*Group Leader*) Naiara **Royo** (*PhD Student*) Eneritz **Rueda** (*PhD Student*) Asier **Ruiz** (*Senior Researcher*) Jaime **Sagarduy** (*General Manager*) María Victoria **Sánchez** (*Senior Researcher*) Víctor **Sánchez** (*PhD Student*) Rafael **Sarría** (*Senior Researcher*) Mari Paz **Serrano** (*PhD Student*) Amanda **Sierra** (*Group Leader*) Virginia **Sierra** (*PhD Student*) Vanja **Tepavcevic** (*Senior Researcher*) Itziar **Terradillos** (*PhD Student*) Jan **Tønnesen** (*Group Leader*) Nerea **Ugidos** (*PhD Student*) Roberto **Valcárcel** (*PhD Student*) Jorge **Valero** (*Senior Researcher*) Koen **Vandenbroeck** (*Group Leader*) Alexei **Verkhatsky** (*Group Leader*) Cristina **Viera** (*PhD Student*) Alazne **Zabala** (*PhD Student*) Fátima **Zallo** (*Postdoctoral Fellow*) Jone **Zuazo** (*PhD Student*) Jose Luis **Zugaza** (*Group Leader*)

Colleagues departing this year

Oihane **Abiega** (*PhD Student*) Alain **Artaso** (*PhD Student*) Mónica **Benito** (*Postdoctoral Fellow*) Tatiana **Gallego** (*Technician*) Jon **Gejo** (*PhD Student*) Haize **Goikuria** (*PhD Student*) Paloma **Gómez** (*PhD Student*) Ricardo **Marticorena** (*PhD Student*) Andoni **Urtasun** (*PhD Student*)

Our researchers published a total of 51 publications in peer-reviewed journals: 45 original articles and 15 reviews. 63% of them have been published by journals in the first quartile.

4. RESEARCH

The strategic research objective of ACHUCARRO continues to be development of co-ordinated and collaborative multidisciplinary research projects to increase our knowledge and understating of the brain functions on all levels, from single molecules, through individual cells and acutely isolated nervous tissues to the brain networks operating in vivo to further advance the discoveries in physiology and pathophysiology of the nervous system.

These are the laboratories and their group leaders at the end of 2017:

Research Groups

*Laboratory of
Axon-Glia
Interactions*



Jimena Baleriola
Group Leader
Ikerbasque Research Fellow

*Laboratory of
Neural Stem Cells
and Neurogenesis*



Juan Manuel Encinas
Group Leader
Ramon y Cajal Fellow

*Laboratory of
Ultrastructural
and Functional
Neuroanatomy of
the Synapse*



Pedro Grandes
Group Leader
Full Professor at the Department of
Neurosciences (UPV/EHU)

*Laboratory of
Memory Circuits*



Mazahir T. Hasan
Group Leader
Ikerbasque Research Professor

*Laboratory of
Neurobiology*



Carlos Matute

Scientific Director and Group Leader
Full Professor at the Department of
Neurosciences (UPV/EHU)

*Laboratory of
**Functional
Neuroanatomy***



Jose Julio Rodríguez Arellano

Group Leader
Ikerbasque Research Professor
(UPV/EHU)

*Laboratory of
Glial Cell Biology*



Amanda Sierra

Group Leader
Ramon y Cajal Fellow

*Laboratory of
**Neuronal
Excitability***



Jan Tønnesen

Group Leader
Ramon y Cajal Fellow

*Laboratory of
Neurogenomiks*



Koen Vandenbroeck

Group Leader
Ikerbasque Research Professor
(UPV/EHU)

*Laboratory of
**GTPases and
Neurosignalling***



Jose Luis Zugaza

Group Leader
Ikerbasque Research Professor
(UPV/EHU)

Research Animals

ACHUCARRO joined the Agreement on Openness on Animal Research, promoted by the Federation of Scientific Societies in Spain (COSCE), with the collaboration of the European Association of Research Animals (EARA), and launched on 20 September 2016.

We are convinced that animal experimentation plays a fundamental role in the discovery of the underlying biological mechanisms of disease, and in the developing of medical treatments. Without research in animals, we would not have most of the medicines, antibiotics, vaccines and surgical techniques that are applied nowadays in human and veterinary medicine.

An important part of the research undertaken at ACHUCARRO aims at contributing to the improvement of human health and wellbeing and is carried out thanks to the use of animals, for advancing in the knowledge of the brain, for finding therapies from brain diseases like Alzheimer, Multiple Sclerosis, Stroke, etc.

The welfare of animals used for research purposes is of paramount relevance for ACHUCARRO, and also the strict compliance and respect to the current legislation on the protection of animals used in research and for other scientific purposes, including education. Our aim is to achieve the highest standards in animal welfare, not only from the point of view of our moral responsibility on them, but also because we are convinced we could not achieve research excellence without proper animal welfare. Our experiments with animals follow the legal standard and are assessed by an Ethics Committee on Animal Experimentation that promotes the use of alternative methods, the reduction in the number of animals used and the refinement in the experimental protocols applied. Not a single research project requiring the use of animals could start without the appropriate and required Ethics assessment and the eventual authorization from the competent authorities.

ACHUCARRO also ensures that the personnel involved in animal care and researchers do have the adequate education and training and the required professional skills, and that all resources are provided to properly keep research animals in terms of facilities, husbandry, wellbeing and veterinary care.

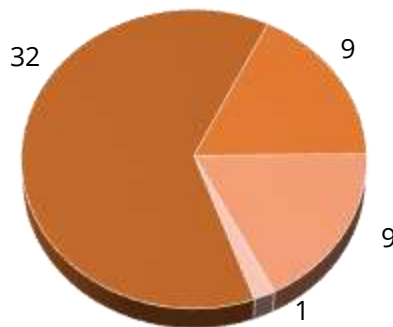
<https://www.achucarro.org/research-animals>



**European Animal
Research Association**

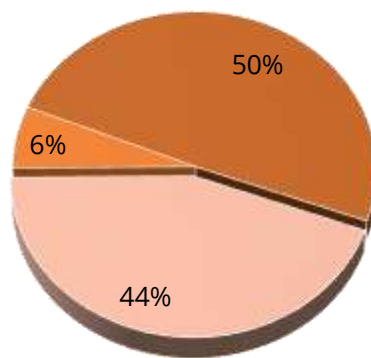


Main output indicators



In the year 2017, we produced a total of 51 research articles.

32 (63%) of them were published in Q1 journals.



A total of 79 different participations in national and international conferences, congresses and seminars.

We presented 39 posters, 35 oral communications and we were invited to give 5 plenary lectures.



We also contributed to the literature of the area with 9 new chapters.

ACHUCARRO is aware of the changes and innovations that are continuously reaching to our sector. According to our policy of research assessment, for instance, we follow the evolution of new ideas like Altmetrics. These non-traditional or non-conventional metric initiatives propose different (alternative) ways to assess the dissemination and impact of research publications.

One of our publications of 2017 reached 106 in this scale, which is an excellent result.



Coupled Proliferation and Apoptosis Maintain the Rapid Turnover of Microglia in the Adult Brain

DOI: 10.1016/j.celrep.2016.12.041

Research Project



NIH R21 Grant awarded to ACHUCARRO and Dartmouth College collaboration project

Rescuing the ApoE4 genotype by activating sterol biosynthesis in the CNS

Alzheimer's disease (AD) is a chronic neurodegenerative disease and a type of dementia. The most common early symptom is the short-term memory loss, the difficulty in remembering recent events. As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, and loss of motivation, not managing self-care, and behavioural issues. In AD, the accumulation of beta-amyloid plaques, the key culprit, disrupts cellular communication and connectivity in the brain by disrupting astrocytic calcium signaling and gliotransmitter release. ApoE4 is a major risk factor for the late onset Alzheimer's disease (AD).

Ta-Yuan Chang, Professor of Biochemistry and Cell Biology at the Geisel School of Medicine of the University of Dartmouth (New Hampshire, USA) and Mazahir T. Hasan, Ikerbasque Research Professor at ACHUCARRO hypothesize that cholesterol-depleted ApoE secreted by astrocyte impairs neuronal functions and boldly propose that correction of this deficiency can serve as a potential treatment and perhaps even a cure for AD.

Cholesterol is important for brain functions, regulating dynamics membrane trafficking to cellular signaling systems, within and between cells. Even though brain represents only 2-3% of total body weight, roughly 25% of body cholesterol is found in the brain. Cholesterol is the building block of different steroid hormones, such as progesterone, estrogen, cortisol, testosterone and vitamin D. Malfunction in brain cholesterol homeostasis can have detrimental effects on brain connectivity, especially communication between astrocytes and neurons. Because dietary cholesterol cannot cross the blood-brain-barrier, our project aims to overcome this problems by genetic control of cholesterol synthesis in neurons and astrocytes, with an expectation that this would help to cure the Alzheimer's disease.

NIH R21 project

2017-2019

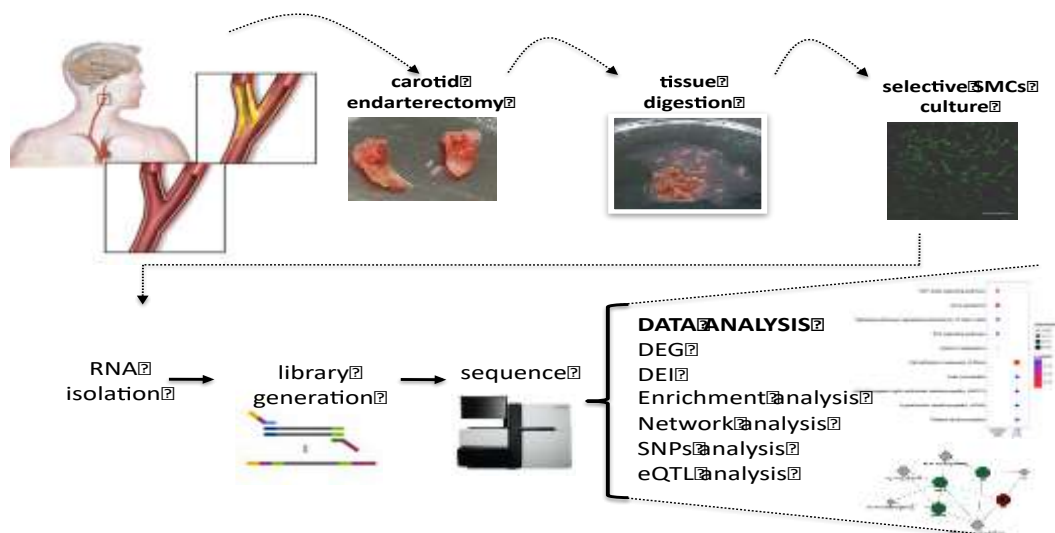
Total funding: USD 392.252,00

Highlights in research outcomes

Identified through the transcriptomic approach RNAseq, 67 genes and 143 isoforms differently regulated in smooth muscle cells (SMCs) isolated from instable carotid atherosclerotic plaques versus stable plaques.

SMOOTH MUSCLE CELLS FULL TRANSCRIPTOMICS ANALYSIS REVEALED BIOMARKERS ASSOCIATED WITH UNSTABLE CAROTID ATHEROSCLEROSIS

Carotid atherosclerosis is a risk factor to develop a cerebrovascular accident. Atherosclerotic plaques can become instable with a tendency to rupture and cause a cerebrovascular accident or remain stable as asymptomatic type. The precise mechanisms by which a plaque becomes unstable are not known. Carotid atheroma plaque is composed by several cell types, among them the smooth muscle cells, which participate in the pathogenesis of carotid atherosclerosis and amount up to 70% of the cellular content of the plaque.



The identification of biological markers that may help to recognize patients with higher risk to develop instable plaques would be of great value for treating and preventing this disease. However, despite intensive research performed during last years, no biomarker with clinical value has been identified. This work is the first full transcriptomic analysis done in SMCs isolated from carotid plaques and has revealed a list of candidate biomarkers, which also have been validated in an additional cohort.

“RNAseq based transcriptomics study of SMCs from carotid atherosclerotic plaque: BMP2 and IDs proteins are crucial regulators of plaque stability” Alloza, Iraide; Goikuria, Haize;

Idro, Juan Luis; Triviño, Juan Carlos; Velasco, José María Fernández; Elizagaray, Elena; García-Barcina, María; Montoya-Murillo, Genoveva; Sarasola, Esther; Manrique, Reyes Vega; Freijo, Maria del Mar; Vandenbroeck, Koen

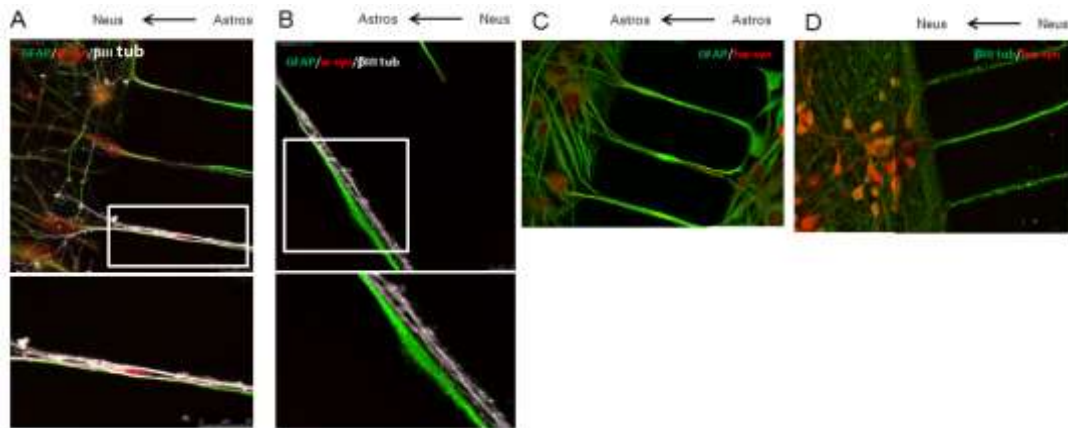
Scientific Reports , DOI: 10.1038/s41598-017-03687-9

Highlights in research outcomes

In vitro α -synuclein neurotoxicity and spreading among neurons and astrocytes using Lewy body extracts from Parkinson disease brains.

A-SYNUCLEIN PRION-LIKE TRANSPORT IN PD IS MEDIATED BY ASTROGLIA

A characteristic hallmark of Parkinson disease is the presence of α -synuclein (α -syn) accumulation in aggregates called Lewy Bodies (LB).



Recently it has been proposed that α -syn can be transported intercellularly triggering neuronal damage, nevertheless uptake and transport mechanisms remain unclear. In collaboration with the Erwan Bezard (University of Bordeaux) we defined the kinetics of neuronal and astrocytic abnormalities induced by human-derived α -syn aggregates derived from LB extracted from post-mortem brains. We then aimed at characterizing uptake and transport mechanisms using primary cultures of cortical neurons and astrocytes either in single well or in microfluidic chambers allowing connection between cells and cell-types. We report that astrocytes take up α -syn-aggregates far more efficiently than neurons through an endocytic event.

Of special interest regarding the disease, we also showed that uptake and spreading of α -syn from astrocytes to neurons can lead to neuronal death by stimulating also endogenous α -syn over-expression. Altogether, we here proposed that astrocytes can act as a buffer by uptaking extracellular α -syn. When α -syn reaches toxic values, it is transported to the neurons where it becomes toxic.

This work is part of the PhD project thesis of Paula Ramos González

"In vitro α -synuclein neurotoxicity and spreading among neurons and astrocytes using Lewy body extracts from Parkinson disease brains" Cavaliere, F.; Cerf, L.; Dehay, B.; Ramos-Gonzalez, P.; De, Giorgi; Bourdenx, M.; Bessede, A.; Obeso, J.A.; Matute, C.; Ichas, F.; Bezard, E. *Neurobiology of Disease*, DOI: 10.1016/j.nbd.2017.04.011

Highlights in research outcomes

Iñaki Paris, Amanda Sierra and Jorge Valero have developed a novel, freely-available tool (ProMolJ) to standardize and accelerate the time-consuming labour of analysis of microglial process motility.

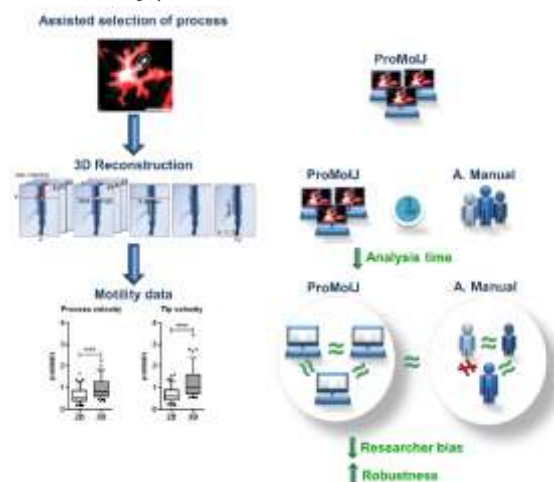
A NEW TOOL TO ANALYZE MICROGLIAL PROCESS MOTILITY

The gold standard technique to study motility involves the use of two-photon microscopy to obtain time-lapse images from brain slices or the cortex of living animals. This technique generates a large amount of 4 dimensionally-coded images which need to be pre-processed to correct technical undesirable artefacts. After pre-processing, images are analysed using different time-consuming and non-standardized protocols which render non-comparable data. Microglial process motility analysis is frequently performed using Z-stack projections with the consequent loss of three-dimensional (3D) information. ProMolJ has been developed to overcome these limitations. ProMolJ is a pack of 5 macros containing all tools required for image pre-processing and motility analysis.

The main core of ProMolJ is formed by two macros that assist the selection of processes, automatically reconstruct their 3D skeleton, and analyse their motility (process and tip velocity). ProMolJ presents key advantages compared to conventional analysis: 1) reduces the time required for analysis, 2) is less sensitive to experimenter bias, and 3) is more robust to varying numbers of processes analysed.

In the study published in *Glia*, ProMolJ is used to show that commonly performed 2D analysis

underestimates microglial process motility, to reveal that only cells adjacent to a laser injured area extend their processes towards the lesion, and to demonstrate that systemic inflammation reduces microglial process motility.



“ProMolJ: A new tool for automatic three-dimensional analysis of microglial process motility” Paris, Iñaki; Savage, Julie C.; Escobar, Laura; Abiega, Oihane; Gagnon, Steven; Hui, Chin-Wai; Tremblay, Marie-Ève; Sierra, Amanda; **Valero, Jorge**

Glia, DOI: [10.1002/glia.23287](https://doi.org/10.1002/glia.23287)

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51. **Impact of Neuroinflammation on Hippocampal Neurogenesis: Relevance to Aging and Alzheimer's Disease**
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Highlight in Engagement

A global initiative that promotes international scientific collaboration between cultures and nations to facilitate innovation, invention and discovery to treat and cure human diseases while at the same time improving human relations for the well-being of humanity and global peace.

“THE SCIENCE BRIDGE” INITIATIVE

122 eminent neuroscientists around the world to announced the launch of an initiative called The Science Bridge, which aims to strengthen ties between scientific research communities in Western and Middle-Eastern/South-Asian countries.

Our colleague Mazahir T. Hasan is the founder of this initiative: *“Scientists, as seekers of knowledge, are the ambassadors of humanity and they can unite the world by harnessing the creative power of cultures and international collaborations to eradicate human diseases”.*



Professor Joshua Sanes, Director of the Center for Brain Science at Harvard stated that *"Anything that can bring neuroscientists together across national, political and religious lines will be a huge help in speeding efforts to understand normal brains and cure sick brains. Harvard neuroscientists in particular have a lot to offer –and a lot to learn. And Hasan's idea that a science bridge could lead to other bridges is especially appealing."*

The Neuron article highlights the successful intercultural exchange of scientific ideas that took place during a *Golden Age* in medieval Arab and Persian cultures—describing this as a historic model of tolerance and free exchange of ideas that the authors hope can serve as an inspiration for those interested in building intercultural bridges through science today.

The Science Bridge initiative calls for the organization of scientific conferences, research exchange programs and shared grants in order to foster new intercultural collaborations, with a particular focus on brain research. It also aims to establish *Twin Institutes*: complimentary research facilities located in both a Middle-Eastern/South Asian country and a Western country.

“Building Bridges through Science”

Lissek et al.

Neuron. 2017 Nov 15; 96(4):730-735. DOI: [10.1016/j.neuron.2017.09.028](https://doi.org/10.1016/j.neuron.2017.09.028)

One of the establishment objectives defined by the Board of Trustees when launched ACHUCARRO was that the centre had to contribute to disseminate and transfer human knowledge, and to spread the scientific culture and literacy. We implement with strategic goal in many different ways, to adapt to the needs and requirements of the different audiences.

5. KNOWLEDGE TRANSFER

Postgraduate education

Achucarro collaborates with three masters programmes organized and coordinated by the University of the Basque Country (UPV/EHU):

- Neuroscience
- Molecular Biology and Biomedicine
- Pharmacology, Development, Assessment, and Rational Use of Medicines

The centre also coordinates the Doctorate Programme on Neurosciences, organized together with the Universities of Coruña (Galicia), Castilla – La Mancha, Pablo de Olavide (Seville), and Rovira I Virgili (Catalonia).

PhD theses



In 2017 a total of 39 PhD thesis projects were progressing in ACHUCARRO, and 2 of them were successfully defended before the end of the year.

Congratulations to our colleagues Oihane and Emanuela.

- ▶ **Oihane Abiega** | Laboratory of Glial Cell Biology
"Mechanisms of regulation of microglial phagocytosis"
- ▶ **Emanuela Gardenal** | Laboratory of Functional Neuroanatomy
"Calcium Sensing Receptor, Calcium Binding Proteins and astrocytic changes in Alzheimer's disease"

Achucarro Seminars

In 2017, we organized 32 Achucarro Seminars.



January 17

A conserved role for Mlc1 in regulating the surface localization of Glialcam from fish to humans

Alejandro Barrallo

U. Barcelona



January 18

Novel Functional Carbon Bio-Interfaces

Maurizio Prato

CIC biomaGUNE (Donostia - San Sebastián)



January 27

The role of neuronal activity in early development of the cerebral cortex

Heiko J. Luhmann

Institute of Physiology, University Medical Center Mainz, Germany



February 3

Adult hippocampal neurogenesis – functional role and regulation by D-cyclins

Anja Urbach

Jena University Hospital (Germany)



February 10

Correlative super-resolution and electron microscopy to resolve subcellular protein localization

José María Mateos

Center for Microscopy and Image Analysis, University of Zürich (Switzerland)



February 17

Inflammation as therapeutic target for Alzheimer's disease

Magdalena Sastre

Imperial College London (UK)



February 24

Shaping the default model of the cortical activity

Maria V. Sánchez-Vives

IDIBAPS - Hospital Clinic (Barcelona)



March 10

Microglial control of neuronal activity and injury: recent lessons and future perspectives

Ádám Dénes

Institute of Experimental Medicine, Hungarian Academy of Sciences (Hungary)



March 29

Network of Neurons and Carbon Nanotubes: interfacing neuronal growth and function

Laura Ballerini

SISSA Trieste (Italy)



April 7

Astrocytes replacement recovers global neuronal synchronizations in Atm-deficient cerebellar circuits in-vitro

Paolo Bonifazi

BioCruces HRI (Barakaldo)



April 12

Hallmarks of Alzheimer's disease in stem cell-derived human neurons transplanted into mouse brain

Amaia Arranz Mendiguren

KU Leuven (Belgium)



April 28

Potential roles of the MicroRNAs in Multiple Sclerosis

David Otaegui

Biodonostia Health Research Institute (Donostia - San Sebastián)



May 12

Myelin Regeneration: From Experimental Models to Multiple Sclerosis Lesions

Brahim Nait Oumesmar

Brain and Spine Institute - ICM Paris (France)



May 19

Mathematical modelling, Bridging the gap between Mathematicians and Experimentalists

Serafim Rodrigues

BCAM (Bilbao)



May 26

Spatial learning, a sculptor of networks

Nora Abrous

Neurocentre Magendie (Bordeaux, France)



May 29

How top wrap the myelin

Tanja Kuhlmann

Institute of Neuropathology, University Hospital Münster (Münster, Germany)



Jul 14

Ciliary receptors modulate neuronal autophagy: impact of amyloid beta

Olatz Pampliega

Université de Bordeaux



Jul 21

Endocannabinoid signaling in multiple sclerosis: new lessons from CB1 receptors in glial cells

Susana Mato

Achucarro Basque Center for Neuroscience Fundazioa



Sep 6

Mechanisms of Associative Learning in Young and Aging Brain

John Disterhoft

Northwestern University (USA)



Sep 7

The myelin mutant taiep rats as a model of progressive multiple sclerosis

José R. Eguibar

Benemérita Universidad Autónoma de Puebla (Mexico)



Sep 15

A walk through adult neurogenesis and image analysis

Jorge Valero

Achucarro Basque Center for Neuroscience Fundazioa



Sep 18

Functional Implications of Neurotransmitter Release by Glial Cells

Maurizio De Pittà

INRIA (Villeurbanne, France) and University of Chicago (US)



Oct 6

Cellular basis for amyloid formation and synapse loss in Alzheimer's disease

Lawrence Rajendran

IREM, University of Zurich (Switzerland)



Oct 20

Glial Lipocalins and the burden of membrane management in the nervous system

Diego Sánchez and Lola Ganfornina

University of Valladolid

Oct 27

Microglial phagocytosis of apoptotic cells is impaired by genetic cystatin b deficiency, a mouse model of progressive myoclonus epilepsy (unverricht-lundborg disease)

Virginia Sierra (Laboratories of Glial Cell Biology. Achucarro Basque Center for Neuroscience Fundazioa)

On-site generation of adult neural stem cells in the postnatal dentate gyrus

Oier Pastor (Laboratories of Neural Stem Cells and Neurogenesis. Achucarro Basque Center for Neuroscience Fundazioa)



Nov 3

Achievements and Unmet needs for Parkinson's disease

José Obeso

HM CINAC (Madrid, Spain)



Nov 10

Inflammation and dysfunctional astrocytes as a cause of human temporal lobe epilepsy

Christian Steinhäuser

Institutes of Cellular Neurosciences, Medical Faculty, University of Bonn



Nov 17

Developmental divergences that contributed to the evolutionary origin of the neocortex

Fernando García-Moreno

Laboratory of Neural Stem Cells and Neurogenesis. Achucarro Basque Center for Neuroscience Fundazioa



Nov 24

Measuring cell metabolism and fuel dependency with the Agilent Seahorse XF Analyzer

Alfredo Caro Maldonado

Agilent Technologies



Nov 29

Neural Interfaces: clinical applications

Ander Ramos

Tecnalia Research and Innovation (Bizkaia) & U. Tübingen (Germany)



Dec 11

Different role of microglia and astrocytes in the onset and progression of nigrostriatal degeneration

Mari Cruz Rodríguez Oroz

University Clinic of Navarra and CIMA



Dec 22

Synaptic dysfunction and neuronal plasticity in motor and cognitive alterations in Huntington's disease: therapeutic perspectives

Jordi Alberch

Department of Biomedicine, Medical School, Institute of Neuroscience. University of Barcelona. IDIBAPS. CIBERNED

Highlights in dissemination outcomes

Congresses and Scientific meetings

In 2017 we organised or collaborated in the organisation of 3 scientific gatherings.

RENA 2017

On May 25th we hosted we first annual meeting of the Spanish Network on Adult Neurogenesis.



EBBS 2017

Form September 8 to 11, members of ACHUCARRO participated in the organisation committee of the 47th European Brain and Behaviour Society Meeting.



SEIC 2017

On November, from the 23rd to 25th, colleagues from ACHUCARRO and the UPV/EHU organised and hosted the 18th annual meeting of the Spanish Society for Cannabinoid Research.



Achucarro Forum

The Achucarro forum conference cycle is an initiative aimed at communication, dissemination and social awareness in relation to research on the brain and its diseases. We are happy to have brilliant partners in this endeavor: the Chair of Scientific Culture of the UPV/EHU and the Basque Broadcasting Company (EITB).

In 2017 the cycle counted with two excellent lectures:



February 23rd
Bidebarrieta Kulturgunea (Bilbao)

Mª Victoria Sánchez-Vives

ICREA Research Professor at the IDIBAPS research centre in Barcelona

Virtual reality and the brain



October 26th
Space DOCK Bilbao (Bilbao)

Josep Dalmau

ICREA Research Professor at the IDIBAPS research centre in Barcelona

Brain, mind and autoimmunity

<https://www.achucarro.org/achucarro-forum/>



Public Outreach and Social Media

On 2017 a group of people of ACHUCARRO pioneered the celebration and commemoration of the Day of Women and Girls in Science in Bilbao, by organising an advocacy and awareness event.

INTERNATIONAL DAY OF WOMEN AND GIRLS IN SCIENCE

The United Nations General Assembly adopted resolution A/RES/70/212 declaring 11 February as the International Day of Women and Girls in Science.

El sábado 11 de febrero se celebra el
Día Internacional de la Mujer y la Niña en la Ciencia

Vente a Happygune, de 10h a 14h para participar
en esta celebración.

Entrada libre, evento gratuito.

Talleres sobre
mujeres y ciencia
para niñas/os
desde 0
hasta 99 años



<http://www.un.org/en/events/women-and-girls-in-science-day/>

Our strategy for social media and information dissemination using the different Internet platforms as a way of increasing our profile with different audiences can be assessed with the following indicators:

Website www.achucarro.org	15 news updates, 32 seminars posted 21,948 visits 79,606 page views 80% new visitors, 20% returning visitors 69% visits from Spain; 31% international 15% of visits from mobile devices
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Twitter AchucarroGlia	1100 followers 6000 tweets and retweets
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Facebook Achucarro.org	429 people engaged (likes) 94 posts
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Students and teachers from Koldo Mitxelena school visited ACHUCARRO (November 30th)

This year has finally been the year of the move to the new headquarters at the Sede Building of the Science Park of the UPV/EHU next to the university campus of Leioa.

6. INFRASTRUCTURE AND EQUIPMENT

On June 21st 2017, the President (Lehendakari) of the Basque Government – Mr. Iñigo Urkullu, the Minister for Education – Prof. Cristina Uriarte, the Rector of the UPV/EHU – Prof. Nekane Balluerka and the Scientific Director of ACHUCARRO – Prof. Carlos Matute officially inaugurated the new headquarters of our centre. The event counted with the attendance of the prestigious and internationally recognised pianist Joaquín Achúcarro, nephew of Nicolás Achúcarro, and closest living relative of the person that gives the name to the centre.

All the authorities and guests highlighted the quality and potential of the new premises, and the continuous support of the regional institutions towards the strategic objectives of our research centre.



From top left to bottom right: Science Park of the UPV/EHU next to the campus; the Sede Building; authorities and guest attending the inauguration.

Currently ACHUCARRO headquarters occupies the whole third floor of the Sede Building, a location property of the public society Science and Technology Parks of the Basque Country. This establishment, within the main campus of the University of the Basque Country is the perfect location for our centre, to make the most of the resources, and the personal and technical capabilities of this environment.

We moved to the new building the equipment and technology that we already had like: *Cellular and Molecular Neurobiology; Primary and Organotypic Cultures; In Vitro Models; Classical Morphometry and Stereology; Immunofluorescence; Immunochemistry and Immunohistochemistry; Electrophysiology; Calcium, Epifluorescence, Advanced Light (Confocal, Super-resolution), and Electron Microscopy; Genotyping and Functional Genomics; Sequencing; qPCR and qRT-PCR; Flow Cytometry and Fluorescence-activated Cell Sorting; Cerebellar Organotypic Culture for Neuroinflammation; Reporter Constructs and Recombinant Expression; and Stereotaxic Surgery and Stereology-based Quantification.*



7. ACHUCARRO IN NUMBERS

STRATEGY AND MANAGEMENT	2014	2015	2016	2017
% of publications in neurosciences over the total in the Basque Country (previous year)	3%	5%	3%	5%
% of publications from Achucarro over the total neurosciences in the Basque Country	38%	22%	36%	20%
H-index of Achucarro	8	10	20	27
% compliance of Management Plan	95%	97%	98%	98%
Number of meetings of the Board of Trustees	2	4	2	3
Annual Budget (million Euros)	1.22	2.20	2.01	1.86
Rate of funding change from Basque Government	25%	20%	24%	24%

PARTNERSHIPS	2014	2015	2016	2017
Number of strategic agreements (accumulated)	5	6	8	5
Number of institutional agreements (accumulated)	6	7	13	18
Number of operational agreements (new)	2	5	1	1

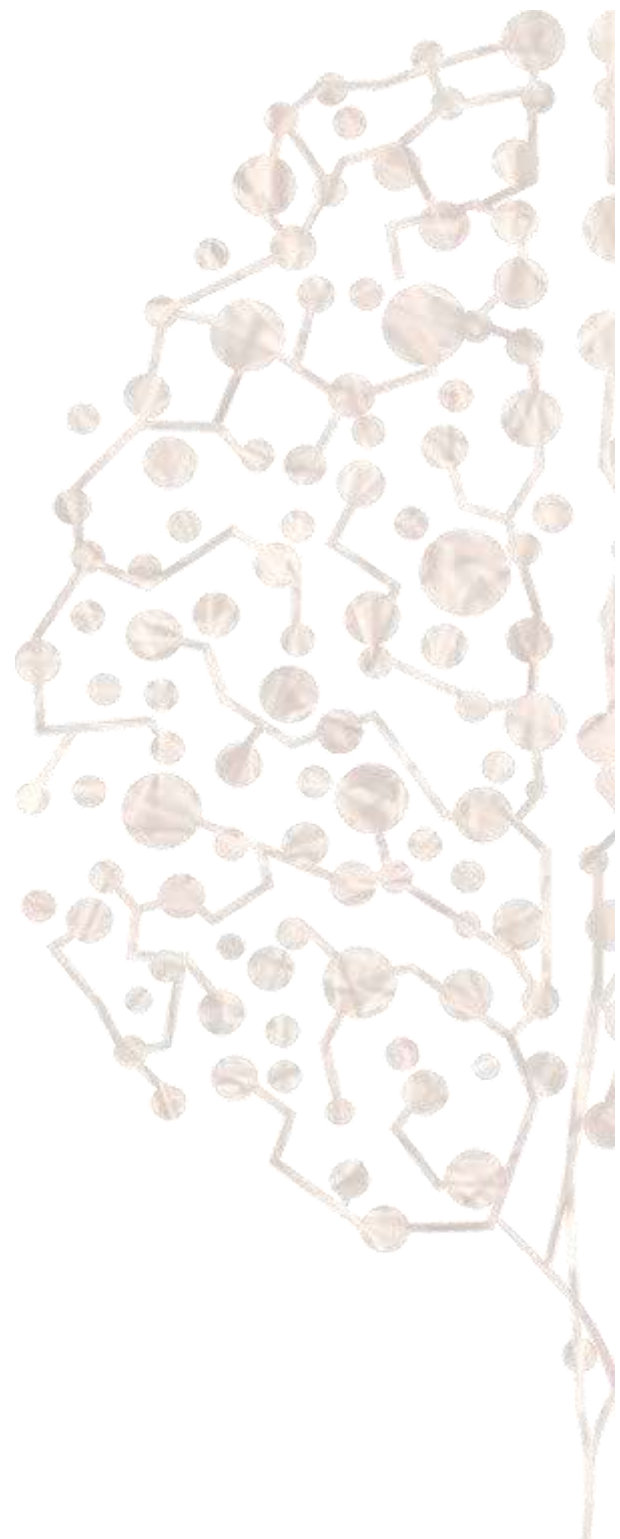
PEOPLE	2014	2015	2016	2017
Number of persons involved in Achucarro	68	73	77	83
Number of directly contracted staff (FDE)	6.5	11.4	16.0	17.49
Number of researchers	63	67	70	75
Number of principal investigators	8	8	11	11
Number of senior researchers	16	20	22	24
Number of postdoctoral researchers	10	10	7	6
Number of PhD students	24	29	30	35
Number of master's students	5	7	14	17
Number of technicians	4	4	4	4
Number of staff	1	2	3	4
Number of Ikerbasque Research Professors	6	6	7	7
Number of Ikerbasque Research Fellows	2	3	5	5
Number of Ramon y Cajal Fellows	1	3	4	4

RESEARCH	2014	2015	2016	2017
Number of research groups	8	8	11	11
Number of publications	45	50	60	51
Number of publications (Q1)	38	38	41	32
Number of participations in congresses	69	96	75	80
Number of books and chapters	16	5	6	9
Number of patents (applications)	0	0	0	0
Number of patents (accepted)	0	0	0	0
Attracted funding (million Euros)	2.2	3.2	2.8	2.0
Number of PhD theses (in progress)	20	29	29	37
Number of PhD theses (completed)	4	4	4	2

KNOWLEDGE TRANSFER/TRAINING	2014	2015	2016	2017
Number of Achucarro seminars	23	22	30	32
Number of congresses, conferences	2	3	2	3
Number of training events	2	1	1	2
Number of dissemination events	2	2	1	3
Number of attendees per event (mean)	190	200	130	170

KNOWLEDGE TRANSFER/DISSEMINATION	2014	2015	2016	2017
Press releases	5	7	5	4
Followers on Twitter	505	793	985	1,100
Tweets on Twitter	2,432	4,134	5,201	6,000
Number of news updates published on the website	28	30	25	15
Total visits to the website	11,849	17,380	21,157	21,948
Visits from Spain	7,897	11,511	13,926	15,228
% visits from Spain	67%	67%	66%	69%
% visits from abroad	33%	33%	34%	31%
Returning visitors to website	43%	40%	42%	20%
Ratio of new visitors to website	57%	60%	58%	80%

INFRASTRUCTURE AND EQUIPMENT	2014	2015	2016	2017
Number of new strategic and singular equipment	4	9	9	2



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