JUNTA DE ANDALUCIA

STRATEGY AND ACTION PLAN 2010/2015

andalusian initiative for advanced therapies

Published by:
Andalusian Initiative for Advanced Therapies

Legal Deposit:
SE-2720/2010

STRATEGY AND ACTION PLAN 2010/2015

andalusian initiative for advanced therapies

EXECUTIVE SUMMARY 06

1. AUTHORS 14

2. JUSTIFICATION 24

3. ANALYSIS OF THE CURRENT SITUATION 30

Cell Therapy and Regenerative Medicine 32

Clinical Genetics and Genomic Medicine 56

Nanomedicine 68

Results transfer 80

Summary of the current situation in Andalusia 92

4. WORKING METHODOLOGY 106

5. MISSION, VISION, STRATEGIC PRINCIPLES AND OBJECTIVES 116

6. ECONOMIC MODEL 124

7. ACTION PLAN 134

Prioritization and strategic forecast 138

Knowledge generation and development of new therapies 141

Results transfer and application 151

Training 156

Communication actions 159

8. EVALUATION OF THE ACTION PLAN 162

9. GOVERNING, ADVISORY AND TECHNICAL COMMITTEES 170

ANNEXE 1. Non-commercial clinical trials with stem cells in Andalusia. 178

ANNEXE 2. Network of health research management foundations in Andalusia 181

ANNEXE 3. Researchers in Andalusia working in the field of advanced therapies 182

ANNEXE 4. Research projects related to A.T. funded by the regional ministry of health. 192

ANNEXE 5. Biotechnology companies from the biomedicine sector in Andalusia. 198

ANNEXE 6. Time line 201

Abbreviations

AEMPS: Spanish Agency of Medicines and Medicinal Devices
CIRM: California Institute for Regenerative Medicine
CRTS: Regional Blood Transfusion Centre
IATA: Andalusian Initiative for Advanced Therapies
IDEA: Agency for Innovation and Development of Andalusia
PI: Principal Investigator
iPS Cells: induced Pluripotent Stem Cells
ISCIII: Carlos III Health Institute
CDTI: Centre for the Development of Industrial Technology
CIBER: Networking Biomedical Research Centre
PRB: Public Research Bodies
FPS: Fundación Progreso y Salud/Progress and Health Foundation
GMP: Good Manufacturing Practice
MICINN: Ministry of Science and Innovation
MIT: Massachusetts Institute of Technology
NEBT: Technology Based Companies
NIH: National Institutes of Health, de EEUU
OTT: Offices of Technology Transfer
IP: Industrial Property Rights
RETIC: Thematic Networks of Cooperative Research in Health
SNS: National Health System
SSPA: Andalusian Public Health System.
ICT: Information and communications technologies
EU: European Union

EXECUTIVE SUMMARY

Background

In recent years, Andalusia has made considerable progress in the field of biomedical research in general, and advanced therapies in particular, thanks to the initiatives of different Andalusian research groups and the progressive sensitization of society and public and private institutions. Ongoing close collaboration has developed between the Regional Ministry of Health and the Regional Ministry of Economy, Innovation and Science with Andalusian Universities, research managers, companies, social agents and the Ministries of Science and Innovation and Health and Social Policy. The efforts made have concentrated particularly, although not exclusively, on developing research programmes in areas related to advanced therapy: Cell Therapy and Regenerative Medicine, Clinical Genetics and Genomic Medicine and Nanomedicine.

Thanks to a favourable, in many respects pioneering, legislative framework, in addition to the budgetary efforts made by the Andalusian Government in recent years and the different agreements reached with other institutions, Andalusia now has a substantial network of infrastructures at the service of biomedical research. Several research centres have been built, some of which specialize in different areas related to advanced therapies, biomedical research institutions, biobanks and a network of public laboratories for manufacturing cell therapy drugs. Andalusia is one of the few Spanish regions where embryonic cell lines have been derived and a special effort has been made to promote translational research, with the Government acting as sponsor in multiple non-commercial advanced therapies clinical trials.

At the same time, we are witnessing the significant appearance of a number of initiatives in many parts of the world and an increase in investments in these research fields, which represent some of the most dynamic areas of clinical research in life sciences. The analysis of other international experiences and the cost and difficulties of research in these areas highlight the need to focus our efforts, to plan appropriately and to allocate resources, if we want to ensure that Andalusia enjoys a prominent position in the area of biomedical research and for this field of study to become one of the revitalizing elements of care quality and innovation, whilst also promoting our business framework and our economy.

Development of the Andalusian Initiative for Advanced Therapies

In October 2008, through the Regional Ministry of Health and the Regional Ministry of Economy, Innovation and Science, the Andalusian Government promoted the creation of the Andalusian Initiative for Advanced Therapies. Its function is to plan the strategy and actions required for the efficient orientation of resources and the fostering of synergies between the programmes for cell therapy and regenerative medicine, clinical genetics and genomic medicine and nanomedicine, whilst also maintaining their particular individual focus, and facilitating the development of new therapies to which the population has fair and equal access.

Throughout 2009, analysis and reflection work has been carried out with the participation of scientific leaders, clinical researchers, research managers, representatives from patient associations and responsible parties from both public and private sectors, inside and outside of Andalusia. The outcomes from this reflection process have shaped the Andalusian Initiative for Advanced Therapies's Strategy and Action Plan for 2010 to 2015 which is set out in this document.

We should not forget that the economic cycle for the development of new therapies, and for their access to the market, will clearly require longer than the 6-year span of this Action Plan. The uncertainties surrounding the evolution of this field of research, its regulation and the possible risks and challenges that have to be faced, make it necessary to delineate the timescale of this Action Plan in order to lay the foundations for its appropriate, smooth development.

However, subsequent reviews of this Plan should follow in the future, with a much broader timeframe in line with requirements of the economic cycle alluded to above.

Mission

The Strategy and Action Plan of the Andalusian Initiative for Advanced Therapies aims to resonate with its mission: "to promote the development of new therapies in order to improve the population's health and to incorporate innovative advanced therapies in the healthcare and progress of our region, by seeking alliances between the academic world, research institutions, health centres, patients' associations, SMEs and the pharmaceutical industry".

The Andalusian Initiative for Advanced Therapies must, therefore, identify, organize and provide the necessary support for the maximum development of multidisciplinary research in the field of advanced therapies in Andalusia. This will require facilitating the training of technologists, basic and clinical researchers, fostering translational research in this field and promoting the generation of a business structure beneficial to such research which will ultimately provide a source of wealth for the region and will enable the potential benefits of advanced therapies to be passed on to the population in as short a time frame as possible.

Overall objectives

The overall objectives underpinning this Action Plan are:

1) **To promote the development and application in clinical practice of new therapies** fundamentally based on research results from Andalusia's three research programmes related to advanced therapies.

2) **To enable fair and equal access in the population** to potential new treatments.

3) **To contribute to the creation of a business environment** which fosters the development of advanced therapies, promoting efficient mechanisms of knowledge transfer and collaboration with the business sector.

4) **To focus efforts.** The ambition of the measures promoted must be to undertake a realistic analysis of the difficulties encountered in this area of research and its cost. For this reason it is necessary to concentrate our efforts on a translational approach, if we wish to create a position of real competitive advantage for ourselves in our region.

5) **To foster synergies** between the three research programmes related to advanced therapies: the Cell Research and Regenerative Medicine Programme, the Clinical Genetic and Genomic Medicine Programme and the Nanomedicine Programme, whose fields of knowledge show increasing overlap.

6) **To facilitate alliances** between all agents involved in the research and development process by encouraging open and transparent mechanisms that enable optimum use of resources and effort in this process, favouring alliances in the national and international sphere.

7) **To promote the translational research approach**, facilitating common instruments of support in the production and application of advanced therapy drugs, in accordance with the requirements of the regulatory bodies.

8) **To facilitate the participation** of scientific leaders in all areas, clinical researchers, research managers and representatives of patients' associations and the private sector.

9) **To identify the needs** of all agents involved in this initiative to develop tools and solutions specific to their own particular needs.

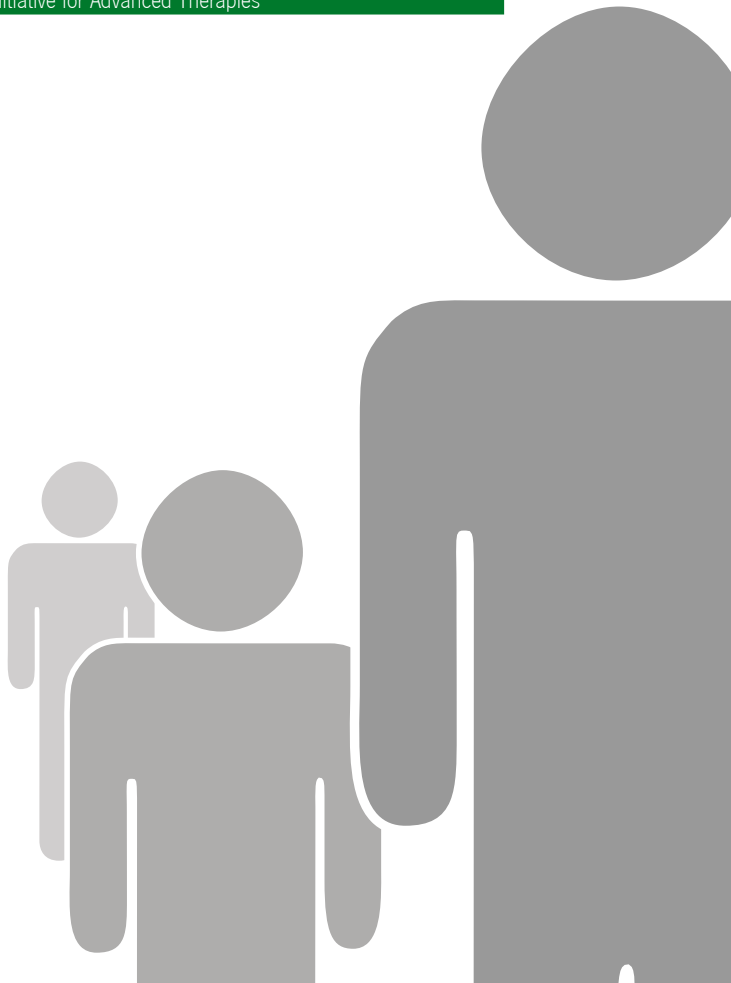
10) **To contribute to the development of an evaluative culture of research and innovation,** which will not only analyse results in the scientific area but also the impact of incorporating these new therapeutic approaches, and the opportunities that may arise from them, in the business sector and the Andalusian public health system.

Access of the population to new therapies and economic model

The course that must be followed to make these new treatments accessible to the population is not yet clearly defined. This is due to the fact that advanced therapies include a whole range of very different possibilities, both from the standpoint of the processing level required and that of the potential risks for their use in humans. In the case of therapies very similar to others already been incorporated in the healthcare system for some years, and where there is no manufacturing process as such, the health system, in collaboration with the Regulatory Bodies, must set out flexible mechanisms that allow the therapies to be incorporated into healthcare with the pertinent quality and safety guarantees. In the case of therapies requiring significant manipulation and a high technological level for their development and manufacturing however, it will be necessary to design effective knowledge transfer mechanisms that will guarantee possible industrial operations, which in turn will ultimately favour the distribution of these products and their accessibility to the population. It is necessary to strengthen the value creation chain spanning knowledge generation to its transfer, fostering the generation of industrial property assets, promoting public-private agreements of collaboration and encouraging the development of an industrial fabric into which technologies or know-how can be transferred .

An economic model supporting our proposal for the management and transfer of results is presented in this Action Plan and is divided into the following areas:

1. Strategic forecast
2. Knowledge generation and development of new therapies
3. Results transfer and application
4. Training
5. Communication actions undertaken by the Andalusian Initiative for Advanced Therapies



Lines of strategy

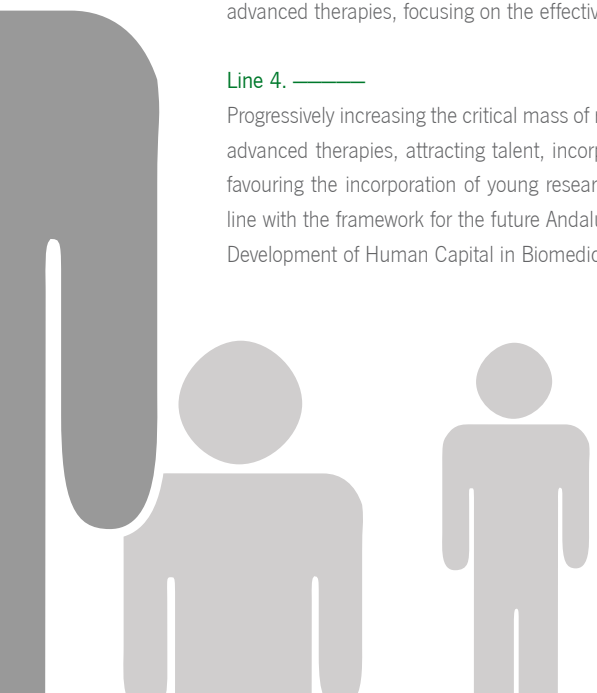
This plan contemplates 86 courses of action structured around 19 strategic lines:

Line 1. ———
Prioritizing those areas which offer both a high potential for social and/or economic return and a sufficient degree of scientific, technical and clinical development within the Andalusian environment.

Line 2. ———
Drawing up an inventory of the infrastructures and equipment available in Andalusia, for the rational and efficient use of resources.

Line 3. ———
Providing Andalusia with the necessary infrastructures and equipment to develop and give support to basic and clinical research in advanced therapies, focusing on the effectiveness of their use.

Line 4. ———
Progressively increasing the critical mass of researchers in the field of advanced therapies, attracting talent, incorporating technicians and favouring the incorporation of young researchers into the system in line with the framework for the future Andalusian Programme for the Development of Human Capital in Biomedical Research.



Line 5. ———
Encouraging the interdisciplinary nature and synergies between the knowledge areas of the 3 Andalusian research programmes related to advanced therapies and between the basic and clinical research teams to enable the translational development of the strategic lines which have been set out.

Line 6. ———
Promoting biomedical research of excellence in areas of maximum interest, together with highly creative unconventional research.

Line 7. ———
Promoting quality clinical trials in areas of maximum interest, keeping equal access criteria for patients firmly in mind.

Line 8. ———
Giving support to clinical research in advanced therapies and the manufacturing of products in research.

Line 9. ———
Developing an active policy to seek public and private funding for projects undertaken within the framework of the Initiative.

Line 10. ———
Promoting mechanisms for the protection and transfer of the results of those lines of short-term research which have been selected by the Andalusian Initiative for Advanced Therapies and which facilitate future clinical application.

Line 11. ———
Promoting mechanisms for the protection and transfer of the results of the medium/long-term research lines selected by the Andalusian Initiative for Advanced Therapies and which facilitate future clinical application.

Line 12. ———
Promoting returns in health and socio-economic terms by encouraging the licensing of protected knowledge or company creation.

Line 13.
Training professionals to manufacture drugs for use in advanced therapies and setting clinical trials in motion with these therapies.

Line 14. ———
Facilitating the training of researchers in the field of advanced therapies.

Line 15. ———
Promoting the training of researchers in laboratory and people management.

Line 16. ———
Disseminating knowledge about the Initiative in the areas of healthcare and academia.

Line 17. ———
Communicating scientific advances in the area of advanced therapies to the general public, distinguishing between new discoveries and possible therapeutic applications, keeping the patients' perspective in mind.

Line 18. ———
Favouring collaboration with scientific journalism.

Line 19. ———
Establishing mechanisms to communicate with patients and to enable their participation in the activities to be carried out by the Andalusian Initiative for Advanced Therapies.

Evaluation

The success of this Action Plan must be evaluated in the long-term according to the number of safe and effective advanced therapies that are finally accessible to the population. The time required for the economic cycle for the development of new therapies, and for their access to the market, is clearly longer than the 6-year time span of this Action Plan. Therefore, these new therapies should be evaluated according to factors which indicate the evolution of the generation and transfer of knowledge to clinical practice and results transfer. A reduced set of indicators has been developed for this task, being selected according to the feasibility of their measurement, making it possible to understand this evolution.

Different committees will take part in the development and assessment process of this Action Plan. Some committees already exist and others, such as the Technical Committee, have been newly created. The indicators will be periodically evaluated by the Andalusian Initiative for Advanced Therapies who will report twice yearly on the development of the Action Plan. This report will be sent to the External Advisory Committee of the Andalusian Initiative for Advanced Therapies which will meet to prepare their conclusions. The report, together with the conclusions of the External Advisory Committee, will be sent to the Governing Committee, which will meet to assess the relevance of introducing modifications to the Action Plan.

1

AUTHORS

Working groups participating in the production of the Action Plan:

1. Knowledge generation: Cell Therapy and Regenerative Medicine

Dr Itziar Ochotorena (Coordinator)
[Manager]
CABIMER-Andalusian Centre for Molecular Biology and Regenerative Medicine
CSIC-University of Seville -UPO- Junta de Andalucía.
Seville

Dr Antonio Bernad
[CSIC Research Professor]
Director of the Regenerative Cardiology Department
CNIC-National Cardiovascular Research Centre.
Madrid

Dr José Becerra
[Professor of Cellular Biology]
Department of Cellular Biology and Genetics
Faculty of Sciences, University of Málaga.
Málaga

Dr Angel Raya
[ICREA Professor - Institució Catalana de Recerca i Estudis Avançats]
IBEC- Institut de Bioenginyeria de Catalunya.
Barcelona

Dr César Trigueros
[Scientific Director]
Fundación Inbiomed.
San Sebastián

Dr José Luis Zugaza
[Deputy Manager]
Andalusian Initiative for Advanced Therapies.
Seville

2. Knowledge generation: Clinical Genetics and Genomic Medicine

Mr Carlos Chinchilla (Coordinator)
[Deputy Technician to the Scientific Production Development Area]
Fundación Progreso y Salud.
Seville

Dr Guillermo Antiñolo
[Director of the Andalusian Programme for Clinical Genetics and Genomic Medicine]
[Director of the Andalusian Genetics Plan]
[Director of the UGC of Genetics, Reproduction and Foetal Medicine]
Hospital Universitario Virgen del Rocío.
Seville

Dr José Antonio Lorente
[Director]
Pfizer-University of Granada-Junta de Andalucía Centre for Genomics and Oncological Research (GENYO).
Granada

Dr Irene Marcos
[Genetics Physician of the UGC of Genetics, Reproduction and Foetal Medicine]
Hospital Universitario Virgen del Rocío.
Seville

Dr José Luis Zugaza
[Deputy Manager]
Andalusian Initiative for Advanced Therapies.
Seville

3. Knowledge generation: Nanomedicine

Dr David Pozo (Coordinator)
[Director. Scientific Production of the Development Area]
Fundación Progreso y Salud.
[Associate University Professor.
Department of Medical Biochemistry and Molecular Biology.]
University of Seville.
[Principal Investigator of the Department of Cell Therapy]
CABIMER-Andalusian Centre for Molecular Biology and Regenerative Medicine
CSIC-University of Seville-UPO-Junta de Andalucía.
Seville

Dr Miguel Blanca
[Head of the Allergology Service]
Hospital Regional Universitario Carlos Haya.
Malaga

Dr Juan Casado
[Associate University Professor. Chemistry-Physics Area]
University of Málaga.
Málaga

Dr José Manuel Domínguez
[Associate University Professor.
Department of Inorganic Chemistry]
University of Granada.
Granada

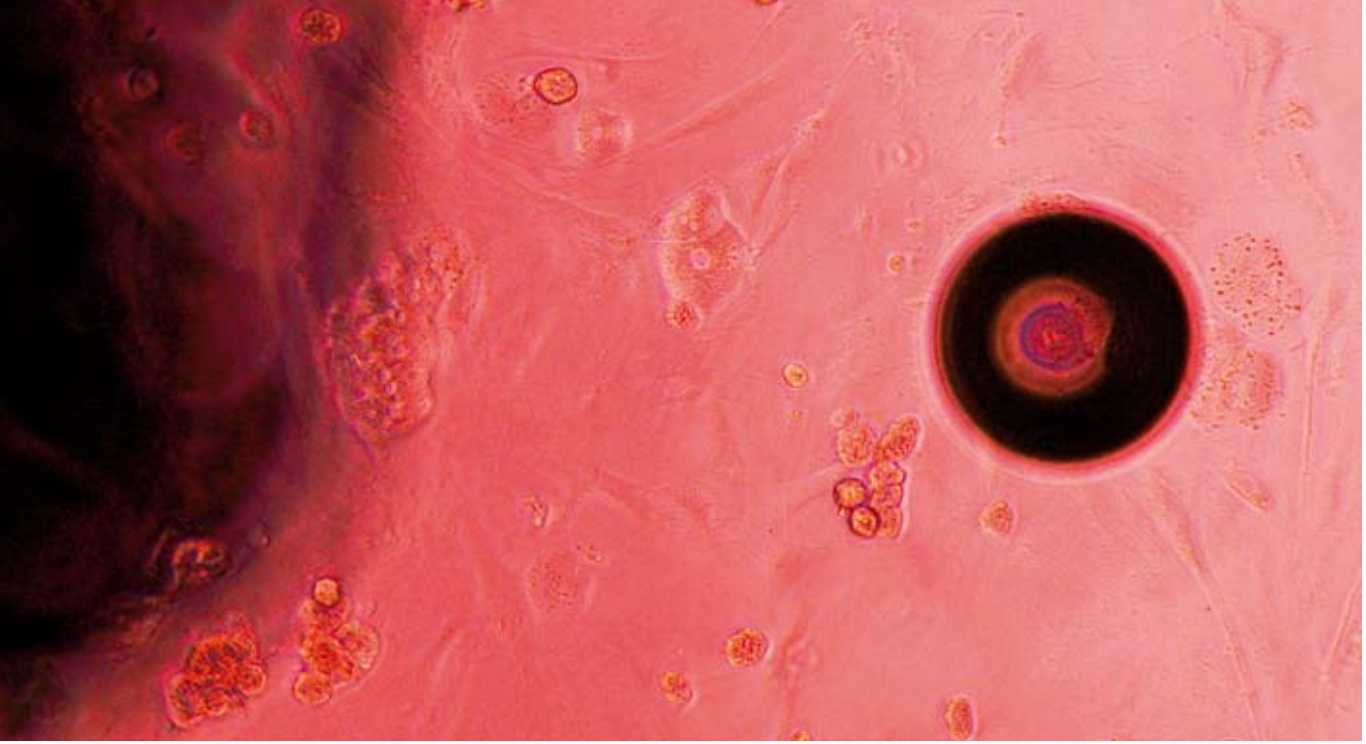
Dr María del Mar Malagón
[Professor of Cellular Biology. Department of Cellular Biology, Physiology and Immunology]
University of Córdoba.
Córdoba

Dr Miguel Alaminos
[Associate University Professor. Department of Histology]
University of Granada.
Granada

Dr Ezequiel Pérez-Inestrosa
[Associate University Professor.
Department of Inorganic Chemistry]
University of Málaga.
Málaga

Dr F. Javier Rojo
[CSIC Associate Scientist]
Institute for Chemical Research-CSIC.
Seville

Dr Paula Zaderenko
[Assistant Lecturer Doctor. Dept. of Physical, Chemical and Natural Systems]
Pablo de Olavide University.
Seville



4. Knowledge dissemination and training

Dr José Luis Zugaza (Coordinator)
[Deputy Manager]
Andalusian Initiative for Advanced Therapies.
Seville

Dr Jorge Alemany
[Ex Vice-president for Strategy]
Cellerix.
Madrid

Dr Eduardo Collantes
[Associate University Professor]
University of Córdoba.
[Head of the Rheumatology Service]
Hospital Universitario Reina Sofía.
Córdoba

Dr Ander Izeta
[Director of the Regenerative Medicine Area]
BioDonostia Institute.
San Sebastián

Ms Belén Jiménez
[Director. Development of Research Resources Area]
Fundación Progreso y Salud.
Seville

Mr. Gonzalo Rivas
[Ex-Secretary]
Andalusian Confederation for people with physical and organic disabilities.
Seville

5. Knowledge application

Dr Inmaculada Herrera (Coordinator)
[Specialist Physician of Haematology Area, Technical Director of the Cell Therapy Unit]
Hospital Universitario Reina Sofía.
Córdoba

Dr Manuel Aguilar
[Director of the Comprehensive Andalusian Diabetes Plan]
[Head of the Endocrinology Service]
Hospital Universitario Puerta del Mar.
Cádiz

Ms Ana Cardesa
[Head of Clinical Trials]
Andalusian Initiative for Advanced Therapies.
Seville.

Ms Gloria Carmona
[Head of Quality and Certification]
Andalusian Initiative for Advanced Therapies.
Seville.

Dr Manuel de la Rosa
[Technical Director. Cell Therapy Unit]
Hospital Universitario Virgen de las Nieves.
Granada

Dr Óscar Fernández
[Head of the Neurology Service]
Hospital Universitario Carlos Haya.
Málaga

Dr Damián García-Olmo
[Head of the Surgery Service]
Hospital Universitario La Paz.
Madrid

Dr Manuel Romero
[Director of the UGC of Digestive Diseases]
Hospital Universitario Nuestra Señora de Valme.
Seville

Dr Antonio Velázquez
[Secretary]
Regional Committee for Clinical Trials.
Seville

6. Knowledge transfer

Mr. Gustavo Fúster (Coordinator)
[Director of the Transfer and Technology Office]
Fundación Progreso y Salud.
Seville

Mr. Eduardo González-Salamanca
[Ex-Director of Business Development for Spain and Portugal]
West Pharmaceutical Services.
Madrid

Mr. Nicolás Ruiz
[Director of the Intellectual Property Department]
Laboratorios Esteve.
Barcelona

Mr. Gerónimo Sánchez
[Clusters Director]
Agencia IDEA.
Seville

Mr. Eduardo Suárez
[Industrial Property Manager]
Genetrix.
Madrid

Dr Neil Thomas
[Director of Business Development and Industrial Property]
Genetrix.
Madrid

Dr José Luis Zugaza
[Deputy Manager]
Andalusian Initiative for Advanced Therapies.
Seville

7. Strategic forecast, funding and assessment of the Initiative

Mr. Gerónimo Sánchez (Coordinator)
[Clusters Director]
Agencia IDEA.
Seville

Mr. Rafael Camacho
[Director-General]
Fundación Genoma España.
Madrid

Dr Cristina Campoy
[Associate University Professor. Department of Paediatrics]
Faculty of Medicine. University of Granada.
Granada

Dr Gloria de la Viña
[Technical Manager for the Biotechnology Sector]
Corporación Tecnológica de Andalucía.
Seville

Dr Jesús Jiménez
[General Manager]
Ingredientis Biotech.
Granada

Mr. Julio Lorca
[Director-General]
Institute for Innovation for Citizens' Wellbeing.
Málaga

Mr. Juan Martínez
[Advisor of the Innovation Observatory]
Regional Ministry of Economy, Innovation and Science.
Seville

Mr. Javier Navarro
[General Manager]
Grupo P-Value.
Seville

Mr. Manuel Rodríguez
[Analysis Director]
Invercaria. Agencia IDEA.
Seville

Dr José Luis Zugaza
[Deputy Manager]
Andalusian Initiative for Advanced Therapies.
Seville

The following people have also participated in preparing the Action Plan:

Mr. Juan Jesús Bandera
[Managing Director]
Fundación Progreso y Salud.
Seville

Dr Rafael Carretero
[Deputy Director-General for Quality and Research]
Regional Ministry of Health.
Seville

Mr. Roke Iñaki Oruezabal
[Assessment and Strategic Forecast Manager]
Andalusian Initiative for Advanced Therapies.
Seville

Dr Jerónimo Pachón
[Director of the Strategic Plan for Research, Development and Innovation in Health]
Regional Ministry of Health.
[Director of the Clinical Unit of Infectious Diseases, Microbiology and Preventative Medicine]
Hospital Universitario Virgen del Rocío.
[Vice-director]
Biomedicine Institute of Seville (IBIS).
Seville

Dr Antonia Aránega
[University Professor. Department of Anatomy and Embryology]
University of Granada.
Granada

Dr Manuel Alonso
[Regional Transplant Coordinator]
Andalusian Health Service.
Seville

Ms Marta Reboredo
[Director of Project Management Area]
Fundación Progreso y Salud.
Seville

Mr. Manuel Arroyo
[Coordinator of the Programmes Area Clusters Management]
Agencia IDEA.
Seville

Dr Pablo Menéndez
[Director]
Andalusian Stem Cell Bank.
Granada

Dr Francisco Martín
[Head of the Cell-Gene Therapy Area]
Andalusian Stem Cell Bank.
Granada

Dr Antonio L. Cuesta
[Principal Investigator]
Fundación IMABIS.
Malaga

Dr Blanca Miranda
[Director]
Transplant Service Foundation and Transplant Coordination Unit
Hospital Clinic de Barcelona.
Barcelona

Dr Verónica Pérez
[Medical and Regulatory Affairs Coordinator]
Andalusian Initiative for Advanced Therapies.
Seville

Dr Ignacio J Molina
[Vice-chancellor of the Health Sciences Technology Park]
University of Granada.
Granada

Dr Bernat Soria
[Director of the Andalusian Programme for Cell Therapy and Regenerative Medicine]
[University Professor. Department of Physiology]
Pablo Olavide University.

[Director of the Stem Cell Department]
Andalusian Centre for Molecular Biology and Regenerative Medicine (CABIMER).
Seville

General coordination:

Dr Natividad Cuende
[Executive Director]
Andalusian Initiative for Advanced Therapies

[Deputy Director]
Regional Transplant Coordination.
Seville

Mr. Francisco Manuel Solís
[Secretary of the Andalusian Plan for Research, Development and Innovation]
Directorate-General for Research, Technology and Enterprise
Regional Ministry of Economy, Innovation and Science.
Seville

Mr. Manuel Ruiz
[Head of Relations with the Health Authorities]
Institutional Relations Unit
Pfizer España.
Seville

Ms Salud Jurado
[Delegate for Andalusia]
Spanish Federation of Rare Diseases (FEDER).
Seville

Dr María Dolores Suárez
[Vice-chancellor of Scientific Policy and Research]
University of Granada.
Granada

2

JUSTIFICATION

Advanced therapies, by which we mean **cell therapy, gene therapy and tissue engineering,** represent an emerging field in biomedical sciences offering new opportunities for the treatment of disease or human body dysfunctions

In recent years, the Regional Ministry of Health and the Regional Ministry of Economy, Innovation and Science, in collaboration with Andalusian universities, researchers, research managers, companies and social agents, have made significant efforts to develop this area of research, principally via the three research programmes related to these types of therapies:

The Cell Therapy and Regenerative Medicine Programme

The Clinical Genetics and Genomic Medicine Programme

The Nanomedicine Programme

The initiatives of several Andalusian research groups, working at the head of national or international projects, have made significant contributions in some of the areas mentioned above. Their efforts, together with the progressive sensitization of society and public and private institutions to biomedical research in general, and to Advanced Therapies in particular, have enabled considerable advances to be made in recent years. Therefore, Andalusia finds itself ideally placed, with **suitable planning and orientation of resources**, to assume a prominent position within the field of biomedical research and for this area to become one of the revitalizing elements of healthcare quality and innovation, whilst at the same time promoting our business structure and our economy.

The ambition of the measures promoted must, nevertheless, be to tackle a realistic analysis of this field of research and its cost. The analysis of other international experiences flags up the need to **focus our efforts** if we really wish to secure for ourselves a position of competitive advantage.

However, the areas of research of the three advanced therapies programmes referred to above are throwing up ever more **points of convergence**. Thus, one of the most promising areas in advanced therapies is the possible development of medicines based on induced pluripotent stem cells (iPS), which were initially developed thanks to the combination of knowledge from cellular biology and genetics. Similarly, research in tissue engineering, where cells are combined with different materials, should be enhanced by the application of nanotechnologies, which also offer new technologies for the localized dispensing of therapies, including gene therapies.

Likewise, the **translational approach** of these three research programmes, with its well-defined aim to achieve clinical application, makes it necessary to promote a team working model which allows ongoing, bilateral exchange of knowledge and information between researchers, practitioners, academia and industry. In addition, this model should promote common support instruments and infrastructures for the production of advanced therapy medicinal products,

in line with the regulatory agencies' requirements concerning therapies which are considered as medicinal products, insofar as they have properties to treat or prevent human diseases, or are able to be administrated to people to restore, correct or modify physiological functions.

Due to the innovative and complex nature and the technical specificity of advanced therapy medicinal products, the European Union has recently developed a specific regulation[1,2], governing the development of these medicinal products, with the aim of guaranteeing their quality and safety. Compliance with this regulation entails a considerable degree of difficulty for reasearchers when transferring their results to clinical practice. For this reason, it is essential to give them the necessary support to allow them to make progress within this regulatory framework which, among other issues, requires that such therapies are produced in pharmaceutical laboratories.

The need for the incorporation of professionals to work in such pharmaceutical laboratories points up common training and educational requirements. A further common requirement of the three research programmes is the need for further effective knowledge transfer mechanisms to enhance the access of the general population to possible new treatments.

The course that must be followed to make these new treatments accessible to the general population has not yet been clearly defined. This is due to the fact that advanced therapies include a whole range of very different possibilities, both from the standpoint of the processes required and that of the potential risks for their use in humans. In the case of therapies that require considerable manipulation and a high technological level for their development and manufacture, it will be necessary to design effective knowledge transfer mechanisms that guarantee possible industrial use, ultimately favouring the distribution of these products and their accessibility to the general population. Nevertheless, in the case of therapies very similar to others that have already been part of healthcare practise for some years, such as

Notes

1. REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union of 10 December 2007.

2. COMMISSION DIRECTIVE 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products. Official Journal of the European Union of 15 August 2009.

the transplant of hematopoietic progenitor cells and where there is no manufacturing process as such, the health system, in collaboration with Regulatory Bodies, should create flexible and speedy mechanisms to govern their incorporation into healthcare practice, with the relevant quality and safety guarantees.

It is for this reason that the Regional Ministry of Health and the Regional Ministry of Economy, Innovation and Science has promoted this Initiative for Advanced Therapies as a tool for the planning of the strategies and actions required for the efficient allocation of resources and to enhance the synergies between the programmes for cell therapy and regenerative medicine, clinical genetics and genomic medicine and nanomedicine, whilst maintaining their particular character, and to facilitate the development of new therapies that are equally accessible to the whole population.

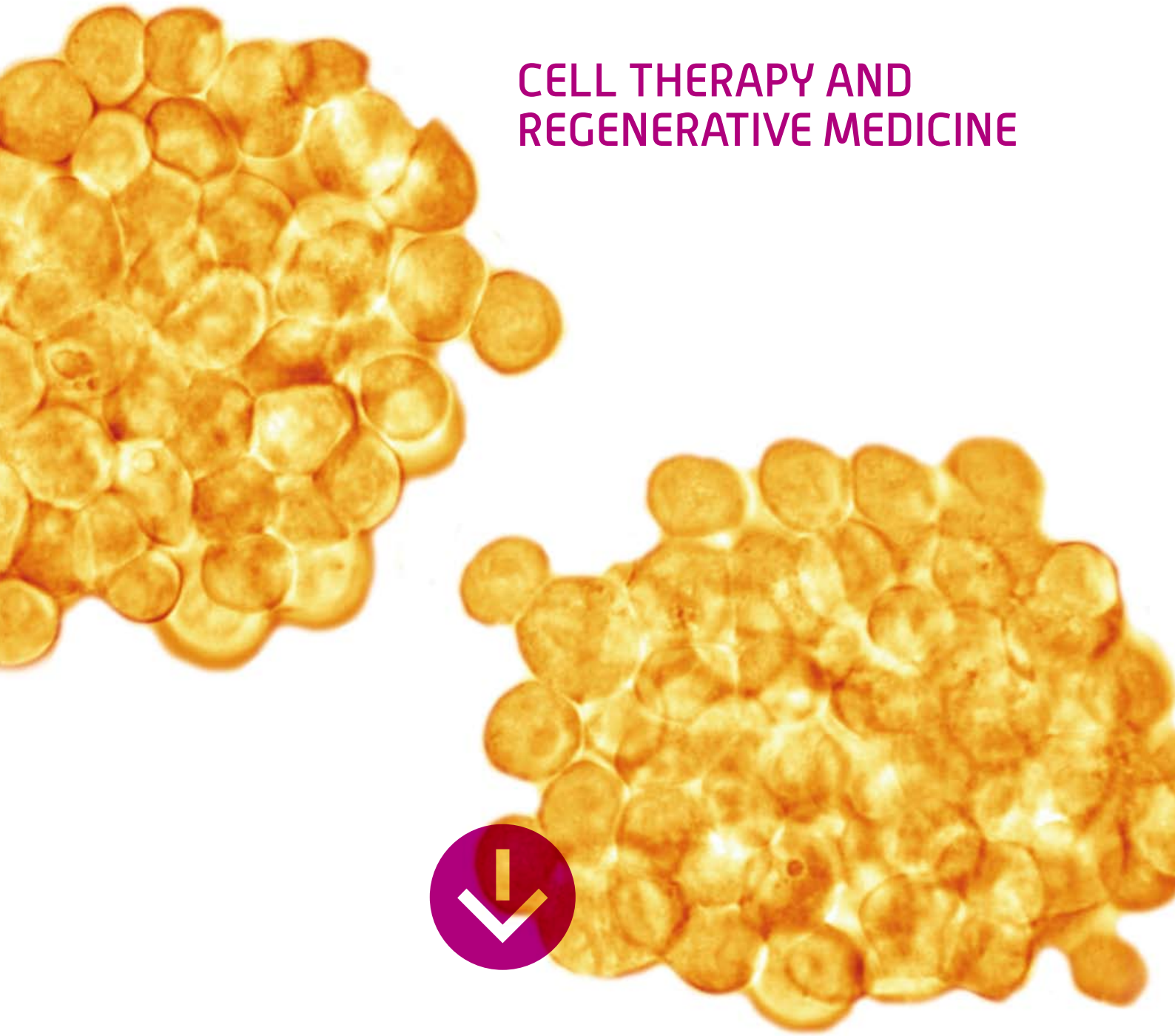
This document, which sets out the strategy and action plan for 2010-2015, has emerged as a consequence of an analysis and reflection process with the participation of scientific leaders, clinical researchers, research managers, representatives from patients' associations and responsible parties from both public and private sectors. Furthermore, the path travelled so far has served to highlight areas where the collaboration of biotechnological and pharmaceutical companies is vital to continued good progress. It is for this reason that we must seek the means to create strategic partnerships in the development of this Initiative.

Finally, we must not forget that the economic cycle for the development of new therapies and to bring them to the market, is clearly longer than the 6-year time scale of this Action Plan. However, the uncertainties around the evolution of research in this field, its regulation and the possible risks and challenges that have to be faced, require us to limit the Action Plan to a period of time in order to develop the research further. However, future reviews of this plan should follow within a much broader timeframe more closely in line with that economic cycle.

3

ANALYSIS OF THE CURRENT SITUATION

CELL THERAPY AND REGENERATIVE MEDICINE



We can define **Cell Therapy** as the use of live cells for the purpose of **restoring or improving** the function of organs and tissues damaged

In summary, we can define Cell Therapy as the use of live cells (whether mature, progenitor or stem cells) for the purpose of restoring or improving the function of organs and tissues that have been damaged, principally, as a result of traumatic lesions, chronic degenerative disease or tumours. Cell Therapy, therefore, constitutes a determining element of what is called Regenerative Medicine.

At present, for developed countries, and increasingly for developing countries, the most important healthcare problems are due to degenerative diseases that affect patients of all ages and not only the elderly, since they are caused, by other etiologies such as genetic disorders, traumatic lesions or some lifestyles, as well as ageing.

A characteristic common to these diseases is that they involve a substantial loss of quality of life and in many cases a loss of life expectancy. In all cases certain types of cells are altered, deficient or absent, causing the dysfunction of the corresponding organ or tissue.

Current treatment for these types of diseases is mainly based on symptomatic treatments that do not bring about the repair of the damaged cells or tissues. In some cases, organ transplant may be a therapeutic alternative, although organ transplants always entail a surgical risk and considerable undesirable secondary effects as a result of tne immunosuppression. Cell therapy is certainly considered a way of repairing tissues via the use of very different cell types that comprise differentiated adult cells, progenitor cells or adult stem cells, both of autologous or allogenic origin, and the first steps have already been taken for the clinical use of embryonic or reprogrammed stem cells.

International Overview of Research in Cell Therapy and Regenerative Medicine

The development of new cell therapies, especially from both embryonic and adult stem cells or, more recently, from Induced Pluripotent Stem Cell (iPS) to treat chronic diseases often affecting large number of patients and for some of which there is currently no effective treatments at present, is highly attractive and a challenge both for the scientific community and for society, the business world and the different Authorities. Therefore, in recent years we have witnessed the significant appearance of initiatives in many parts of the world and an increase in investments in this field. Stem cell research, therefore, represents one of the most dynamic areas of life science research.

There are currently important research groups active in the USA and in many countries in Europe and the Asian Pacific area, which are jockeying for position.

Below, we include a table with a list (not exhaustive) of some of the most outstanding international research centres in this area

(Spanish centres are not included as they are shown in the national overview).

GERMANY

Munich

Institute of Stem Cell Research
Neuronal, haematopoietic, pancreatic and liver stem cells

Bonn

University of Bonn
Reconstructive neurobiology: neuronal stem cells, neural regeneration; and cell engineering

Leipzig

Traslational Centre for Regenerative Medicine
Tissue engineering and biomaterials; replacement cell therapy, distribution systems

CANADA

Toronto

McEwen Centre for Regenerative Medicine
Regenerative medicine in heart, diabetes, neurodegenerative diseases and cell reprogramming

U.S.A.

Nashville

Vanderbilt Center for Stem Cell Biology
Embryonic stem cells and diabetes

Massachusetts

Harvard Stem Cell Institute
Cell development and regeneration, epigenetics of stem cells applied to cancer, cardiovascular, diabetes, neurodegeneration and liver

La Jolla

Salk Institute
Genetic stability and stem cells in the aging process and its pathologies

Minnesota

Stem Cell Institute - Minnesota
Embryonic iPS, beta cells for diabetes, cardiovascular, neural and muscular stem cells

Berkeley

Berkeley Stem Cell Center
Development of new cell therapies

New Haven

Yale Stem Cell Center
Genomic and dynamic stability of chromatins in stem cells, niches of stem cells and homing; transcriptional regulation in stem cells and progenitor cells, cancer stem cells, tissue engineering, biomedical engineering

Los Angeles

The UW–Madison Stem Cell and Regenerative Medicine Center
Neural regeneration, cardiac regeneration, haematopoietic stem cells, generation of pancreatic cells, tissue engineering and cancer stem cells

The Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research
Regenerative medicine: embryonic stem cells in neurobiology

Ohio

National Centre for Regenerative Medicine
Adult and embryonic stem cells for their use in therapy: Fat, embryonic, haematopoietic, iPS, mesenchymal, neural and umbilical cord stem cells

Pittsburgh

McGowan Institute for Regenerative Medicine
Functional restoration by the combination of cells and materials (bio-organs), functional re-establishment of the tissue/organ (artificial organs), tissue engineering and combined gene and cell therapy

FRANCE

Paris

Institut Pasteur
Stem cells and development

ITALY

Milan

University of Milan
Biology and pharmacology of stem cells in neurobiology

ISRAEL

Haifa

Rapport Institute
Immunology of stem cells, cardiovascular biology, neurosciences, stem cell genetics

Jerusalem

The Haddash Human Embryonic Stem Cell Research Centre
Properties of embryonic stem cells, use of stem cells in transplants and in gene therapy

JAPAN

Kofu

Nichi in Centre for Regenerative Medicine
Corneal limbus, retinal, hepatic and endothelial cornea stem cells

NORWAY

Oslo

Norwain Centre for Stem Cell Research
Involvement and biology of stem cells in cancer

SINGAPORE

Singapore

Genome Institute of Singapore
"Stemness", differentiation, cell reprogramming

SWEDEN

Lund

Lund Stem Cell Centre
Molecular regeneration in haematopoietic and neuronal stem cells; gene therapy

Stockholm

Karolinska Institute
Embryonic stem cells in neurobiology

UNITED KINGDOM

Cambridge

Cambridge Stem Cell Initiative
Neural repair, pluripotent cells and cancer stem cells

The Wellcome Trust Centre for Stem Cell Research
Niches of stem cells, intracellular signalling, reprogramming and epigenetics, cancer stem cells

Sheffield

Centre for Stem Cell Biology
Characterization, genetic stability and differentiation in stem cells

London

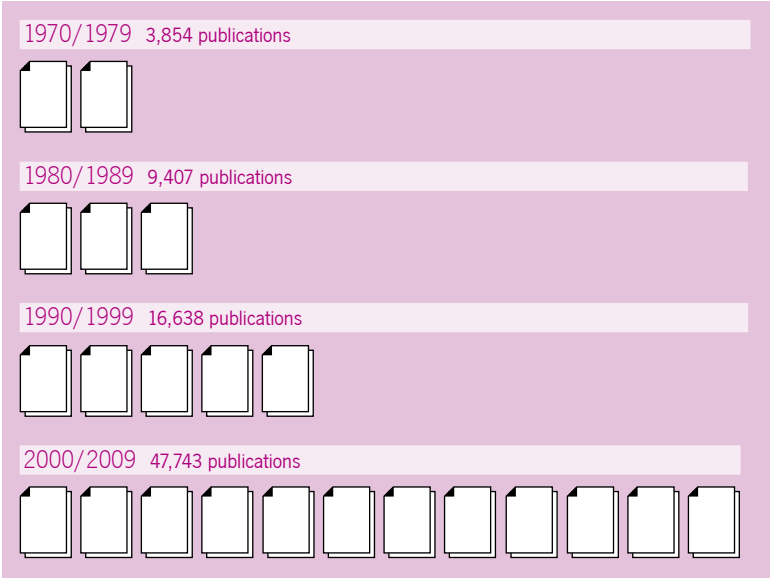
The UCL Centre for Stem Cells and Regenerative Medicine
Characterization of stem cells and their application in areas: cardiovascular, hepatic, respiratory, haematological and cancer

Edinburgh

Centre for Regenerative Medicine
Stem cells and their niches, and self-renewal of stem cells

Stem cells publications

Source: Own preparation. The number of publications has been obtained from pubmed with the search criteria "Stem Cells" as MeSH Major Topic.



In this sense it is surprising to see the exponential growth of **research activity** in stem cells, which gives an idea of the relevance this field has taken on in recent years, as can be seen in the graph that represents the number of publications on stem cells since the 1970s.

This increase in research activity is largely promoted by the support of some governments who are investing large sums of capital to push forward rapid progress in this research field. USA, United Kingdom, China, Israel, Singapore and South Korea are some of the countries with significant governmental support.

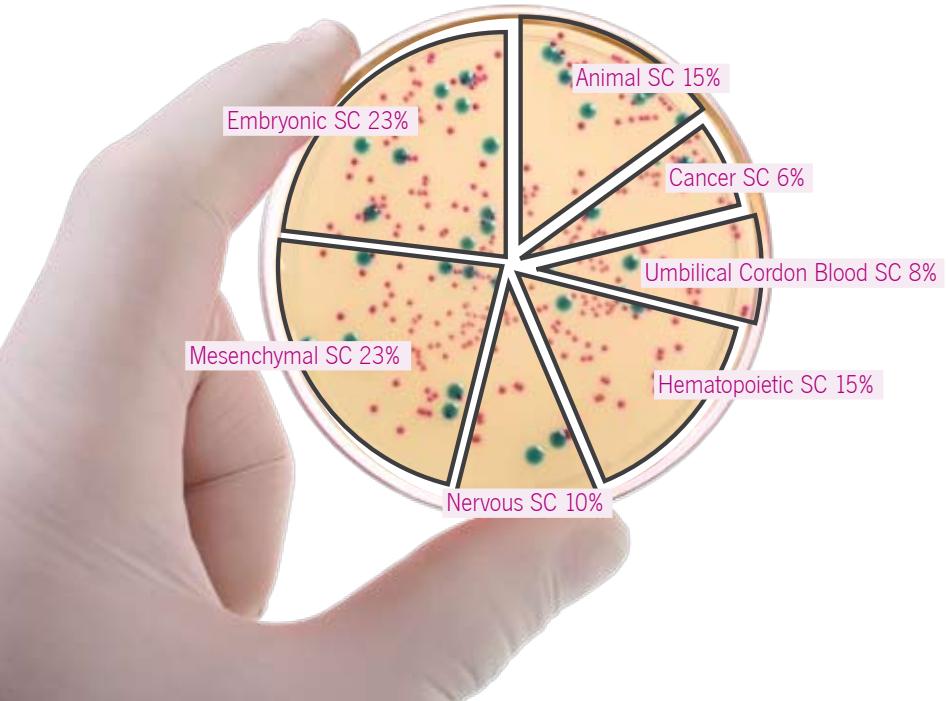
The **US government**, for example, allocated around $550 million to stem cell research in 2004. Given the federal restrictions on embryonic stem cell research in place at that time, only $24 million were allocated to stem cell from this source, an amount slightly lower than that of other countries with much lower budgets but where research is being promoted. However, the recent abolition in the USA of the presidential veto on public funding of research into embryonic cells has changed the outlook.

Additionally, some States within the USA are allocating considerable investments to this area of research. For example, in 2004, **California** decided to earmark $3,000 million for stem cell research during the following decade, through the California Institute for Regenerative Medicine (CIRM). At the start of 2009, the CIRM had already allocated over $500 million to funding research projects with a further $300 million as loans. A further $1,150 million had already been authorized for the building of infrastructures devoted to stem cell research. This development is expected to be finished in 2010. In 2009, the CIRM also focused on promoting clinical trials in their early phases,

allocating $60 million to funding translational research together with an additional $210 million for grants and loans to multidisciplinary teams, whose activity is centred on developing cell therapies to implement phase 1 clinical trials.

In the case of the **United Kingdom**, public funding of stem cell research amounted to £40 million (approximately €57 million) from 2002-2004, allocated to the following areas: basic embryonic and adult stem cells research, clinical research aimed at therapeutic applications, applied stem cell research related to engineering and physics (scientific materials, cryopreservation, etc.), areas related to regulation and responsibility, general perception and social implications, marketing and its implications or barriers, translational research and study of international dynamics and also to the development of large-scale technology. Between 2005 and 2015, it has been estimated that the United Kingdom will invest between £41-104 million per year (approximately between €59 million and €159 million per year) allocated to: fostering public-private association for the development of predictive toxicology tools from stem cell lines, strengthening the necessary infrastructure for the development of therapies from stem cells (excellence centres, United Kingdom stem cell bank, cell therapy production units), consolidation of research funds, extension of regulatory measures favourable for clinical applications and the establishment of a national cooperative stem cell network.

The cell types most frequently studied or used, both in research and commercial activity, are shown in the following chart, obtained from the market research carried out by Select Biosciences in 2007. Almost a quarter are working with embryonic stem cells and another quarter concentrate their efforts on mesenchymal cells.



Emerging use of the different types of stem cells at present

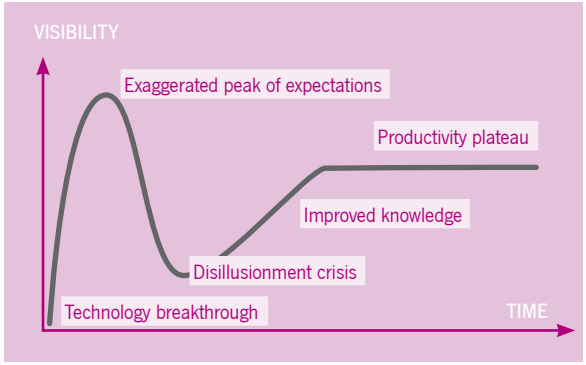
Adapted from: *Stem Cell 2007 Industry Analysis Report (Select Biosciences)*

Since November 2007, with the publication of the preparation of human Induced Pluripotent Stem Cell (iPS) from human fibroblasts by the groups of Dr Thompson, from the University of Wisconsin-Madison, and Dr Yamanaka, from the University of Kyoto, this cell type is the subject of intense international research, being considered as one of the areas of greatest interest. In the last 2 years alone, over 750 studies have appeared on this new technology in pubmed *(search criterion: iPS in Title/Abstract and between 01/11/2007-31/01/2010)*.

The expectations generated by the therapeutic potential of stem cells has undergone significant variations since, in 1998, Dr Thomson's group isolated and cultured human embryonic stem cells. The initial great expectation surrounding embrionic stem cells due to their potential to differentiate into any other cell type, faced multiple technical, legal and ethical difficulties with regard to the development of therapies. In parallel with this, research into possible therapeutic applications with adult stem cells has increased. This research has also had to face technical and regulatory difficulties, as discussed below. Analysis of the variation in these expectations fits in with the **Gartner cycle**, described by the analysis firm Gartner Group observing emerging technologies. The model represents the evolution of what is called the "visibility" of an emerging technology (although it would be more correct to call it "expectations raised by that technology") over time.

The evolution progresses from a peak of exaggerated enthusiasm, followed by a period of disillusionment, finally plateauing out with the eventual understanding of the technology and of its role in the market. Possibly, the stem cell field is currently in its fourth stage, where expectations of the technology have been revived, albeit with greater moderation.

The difficulties associated with development in this field of research and its application may possibly have restricted it to the academic area and biotechnological SMEs, although in recent years there has been growing interest shown by the pharmaceutical industry or "Big Pharma". In that regard, the first experience of public-private consortium occurred in October 2007 between Glaxo-Smith-Kline, Astra-Zeneca, Roche and departments of the



British government. It was very significant in November 2008 that the pharmaceutical company Pfizer announced the creation of a research unit specifically devoted to regenerative medicine, Pfizer Regenerative Medicine, with a head office in the USA and another in the United Kingdom.

The analysis of **patents** related to stem cells in 2005 produced striking results. Public institutions made up 44% of the patent holders, with the private sector accounting for the remaining 56%. In such instances, public institutions would generally represent a much lower percentage. In terms of patent registration countries, USA secured 51%, followed by the United Kingdom, Canada and Germany, with 4% each, and Australia with 3%[3].

There are 3 main reasons for this expectant attitude in recent years by the "Big Pharma":

1. The legal and regulatory framework of cell therapy is undergoing fast modifications and has a complex interpretation, making judicial resolution relevant in the case of any conflicts that may arise.

2. There are difficulties in reproducing the results obtained in the experiments.

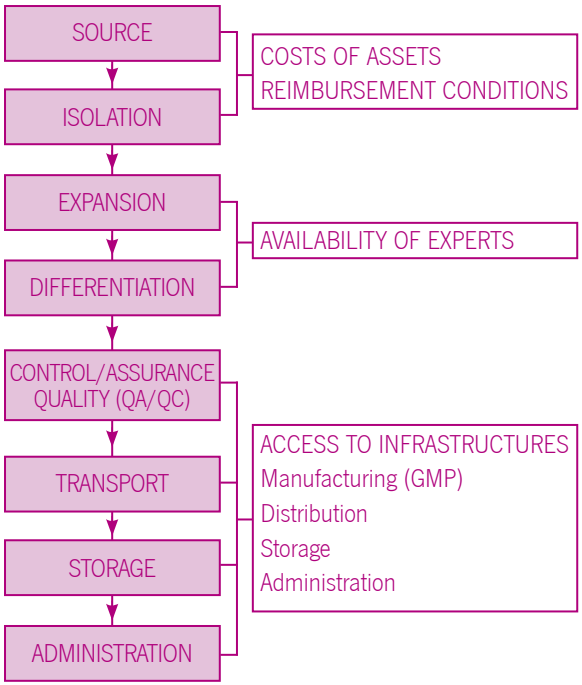
3. There are limitations arising from scaling up production. It is, therefore, necessary to concentrate research efforts in this field.

Notes

3. Data presented in the World Stem Cells and Regenerative Medicine Congress, held in London in May 2009.

In fact, although it is true that research activity in this field has multiplied exponentially in recent years, it is also true, as has been previously mentioned, that there are multiple **difficulties** that must be negotiated in order to make the necessary leap which will turn this research into effective treatments of benefit to the general population within the next few years.

Challenges in Cell Therapy



Both scientific and financial challenges must be tackled. These challenges arise from the regulation of this type of research and from the potential risks derived from the therapies themselves. The main difficulties that must be overcome are:

A. SCIENTIFIC DIFFICULTIES:

- Limited understanding of the biological regulation underlying the processes of expansion, differentiation, migration, survival, etc. of the stem cells and cells derived therefrom; as well as of their interaction with the niche in physiological conditions and tissue damage repair conditions.

- Difficulty in administering stem cell-based therapies specifically aimed at human body targets, avoiding undesired effects in other areas of the body. There is uncertainty regarding the biodistribution of cells and how to guarantee that they can be safely and effectively transplanted.

- Uncertainty regarding the capacity of cells to maintain their functionality after expansion and differentiation *in vitro*, and how to accurately predict effects before starting the clinical trials (difficulty in defining dose, potency, etc.).

- Problems of production scaling and reproducibility of growth in several types of stem cells. Given that most research is still in the early stages of development, the problem of production on a greater scale has still not been resolved.

- Development of technologies that enable a better view of cells transplanted *in vivo*.

B. FINANCIAL DIFFICULTIES:

- The long and difficult road towards clinical application, which requires: standardized procedures to obtain and use stem cells; a greater understanding of the relevant risks and benefits; a greater understanding of the action mechanism; regulatory systems congruent with all stages of development; recognition of the key requirements for entering the field of commercial innovators, length of time for potential research to become approved therapies.

- There is a division between cell therapies derived from embryonic and adult stem cells in terms of acceptance by some sectors of society from an ethical standpoint, in interest and commercial viability and in the development and progression to clinical research.

- The absence of reliable clinical data hinders the investment in embryonic stem cell research, despite the promising outlook.

- Commercial advantages are expected in countries with permissive regulatory systems, but they are not guaranteed.

- The inherent logistical difficulties with these fragile products with a short average life, involve high production costs which, in some cases, may be difficult for the health systems to assume. For example, the autologous use ("personalized") of stem cells for certain indications generates questions with respect to the feasibility of their use in the light of cost-benefit analysis.

C. REGULATORY DIFFICULTIES:

- There are important loopholes in the field of regulation, particularly within the European Union, and application standards are not identical in Europe, the USA and Japan.

- The high standards and requirements imposed by current regulation may unsustainably increase the cost of research and development and hinder patients' access to new therapies. On the other hand, it is necessary to be careful since uncontrolled clinical trials do not generate useful data and, furthermore, there is the risk of creating great social alarm in the event that serious secondary effects appear due to the unethical, unsuitable application of advanced therapies or where the minimum quality and safety criteria are not adhered to.

- Current regulation, classing cells with conventional medicinal products, may favour the large pharmaceutical companies, disadvantaging the initial clinical progress generated by the initiative of non-commercial sponsors (from the academic and hospital world).

D. POTENTIAL RISKS:

- Risk of transmission of pathogens, tumour generation and risks derived from immune response, especially in allogenic therapies, which require the optimization of immunosuppressant medicinal products.

- Risks derived from the cell production process which must be carried out in GMP environments (EU Good Manufacturing Practices).

- Need to develop culture systems that reduce, or avoid insofar as possible, the use of animal proteins due to the possibility of transmission of pathogenic agents.

- Safety and efficacy must be demonstrated in carefully designed and ethically solid clinical trials.

Another crucial aspect for the development of stem cell-based therapies is the support required to develop translational research in this field, overcoming the so-called "valley of death" between the basic clinical research results and the development of new therapies. This period covers preclinical research and the first phases of clinical research, where there are fewer funding possibilities.

Despite this, the number of clinical trials with different cell therapies has increased in recent years. Below, we show the number of clinical trials registered in clinicaltrials.gov with one of the cell types that are being tested most: mesenchymal cells.

In April 2010, the number of clinical trials registered came to 99, of which 8 corresponded to phase III tests in pathologies such as defects in articular cartilage, critical limb ischemia, graft-versus-host disease, Crohn's disease and correction of bone defects in benign tumours.

These trials are mainly being carried out in the USA, Europe, Middle Eastern countries, India and Canada. It is particularly striking that the numbers of trials in China, almost equals that in Europe as a whole. Many of these trials, unlike other medicinal products, are performed by public institutions or with governmental funds.

Clinical trials using embryonic stem cells have not yet been performed. In January 2009, the FDA approved the first clinical trial, requested by an American company, with nerve cells obtained from embryonic cells in patients with medullary lesion. However, this trial has not yet started recruitment since the FDA requested a review of some aspects related to the preclinical trial carried out and some of

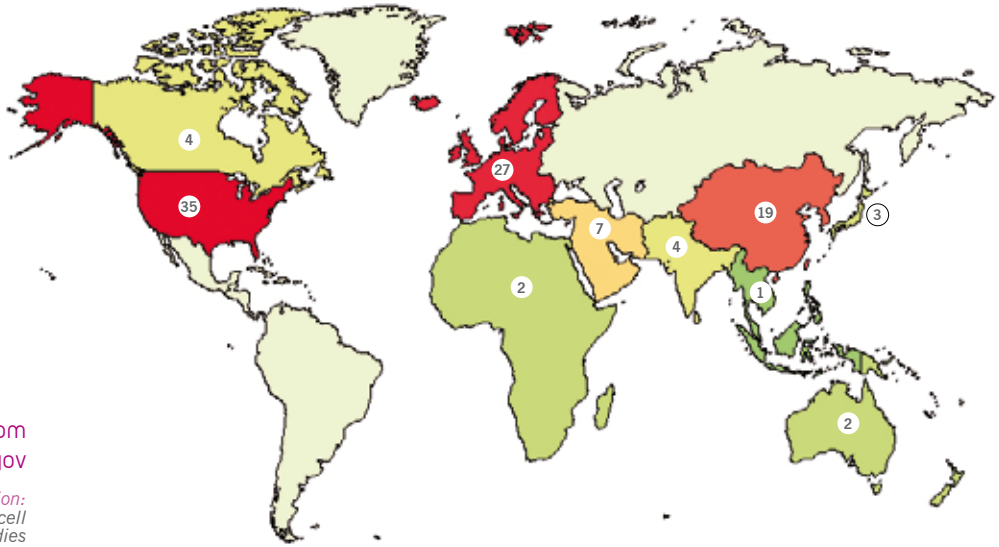


Image obtained from www.clinicaltrial.gov

search criterion: mesenchymal stem cell Interventional Studies

the adverse effects observed in it. In November 2009, another American company also requested the approval of a clinical trial with retinal cells derived from embryonic cells for the treatment of Stargardt's macular dystrophy. This request, too, is awaiting FDA authorization.

The creation of biotechnology companies in the sector, however, shows a different pattern, with the USA predominating, making up 56% of these companies, followed by the United Kingdom with 19%. In the rest of Europe, we have 14%, and the remainder are distributed between Canada, Asia and the Middle East[4].

Notes

4 Data presented in the World Stem Cells and Regenerative Medicine Congress, held in London in May 2009.

5 ACT 7/2003, of 20 October, regulating research in Andalusia with human pre-embryos, not viable for in-vitro fertilization. BOJA (Official Journal of the Andalusian Autonomous Government) of 31 October 2003.

6 ACT 45/2003, of 21 November, amending Act 35/1988, of 22 November, on Assisted Reproduction Techniques. BOE (Official State Gazette) of 22 November 2003.

7 ACT 14/2006, of 26 May, on human assisted reproduction techniques. BOE (Official State Gazette) of 27 May 2006.

Spanish Overview of Research in Cell Therapy and Regenerative Medicine

In Spain, Andalusia was the first autonomous region to approve legislation regulating embryonic stem cell research in October 2003[5]. In January 2004, the Cell Line Bank, the seed of the current Andalusian Stem Cell Bank, was opened in Granada. In November 2003, Act 45/2003[6] was approved at national level, also permitting the use of pre-embryos for research purposes but on a much more restrictive basis. It also stipulated the need to create a National Cell Line Bank. This bank was established within a network composed of three nodes, in Barcelona, Valencia and Granada, the latter being the central node. Later, in January 2010, a fourth node was incorporated in San Sebastian, although exclusively with adult stem cell lines. This regulation was replaced by Act 14/2006[7] which laid down less restrictive criteria for the use of these pre-embryos for research purposes.

In recent years we have witnessed increasing **research activity** in this field, with the establishment of important research centres, such as the Barcelona Centre for Regenerative Medicine, the Andalusian Centre for Molecular Biology and Regenerative Medicine in Seville, or the Príncipe Felipe Research Centre in Valencia.

SPAIN

Barcelona

Barcelona Centre for Regenerative Medicine
Pluripotency of stem cells; Differentiation of embryonic stem cells; Regeneration, development of the heart in vertebrates; Left-right patterning; Development of limbs as growth model, establishment of tissue models and cell differentiation.

Seville

Andalusian Centre for Molecular Biology and Regenerative Medicine
Cell therapy applied to diabetes and neurodegenerative diseases

Granada

Andalusian Stem Cell Bank
Biology of Reprogramming and retrotransposition; Embryonic, haematopoietic and mesenchymal stem cells; Cell-gene therapy

Valencia

Príncipe Felipe Research Centre
Cell Therapy; Reprogramming and biohybrids; Molecular neuroendocrinology; Biomaterials; Biology of the Stem cells

San Sebastian

Fundacion Inbiomed
Cell therapy of cardiovascular diseases and neurodegenerative diseases, tumour stem cells. Manufacturing of engineered skin as a product under research for the treatment of epidermolysis bullosa

There is also a telematic Cell Therapy network in the **Carlos III Health Institute**, the TERCEL network, in which 27 research groups from Madrid, Andalusia, Catalonia, the Region of Valencia, Castilla-Leon, Navarre, Galicia, Extremadura and Murcia, participate, with the collaboration of researchers from the Basque Country in one of the groups located in Madrid.

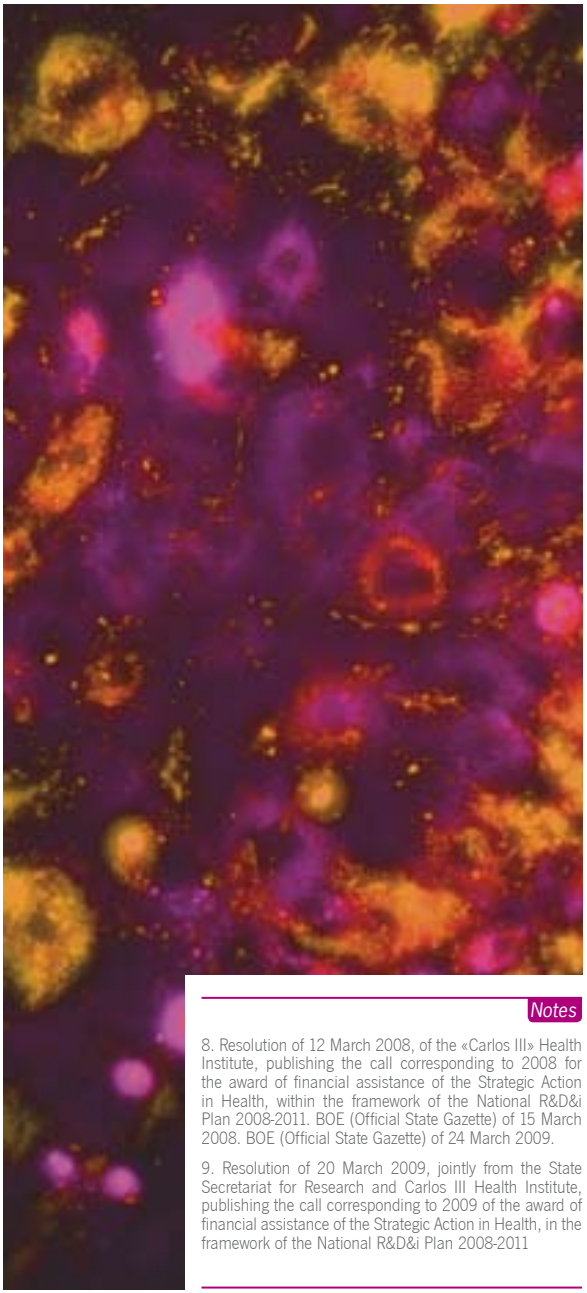
With respect to **clinical research**, several clinical trials with adult stem cells have started in Spain. These trials are currently in different development phases. Most are being carried out in the public sector in autonomous regions such as Castilla-Leon, Navarre, Asturias, Catalonia, Basque Country, Madrid or Andalusia. In the private sector, the role of the company Cellerix is particularly noteworthy with two phase

III clinical trials of their product, based on autologous mesenchymal cells for the treatment of perianal fistulas of different etiology and a phase II clinical trial with engineered skin for the treatment of epidermolysis bullosa.

National public funding has also increased in recent years. In October 2007, the Council of Ministers approved the Ministry of Health and Consumer Affairs' Advanced Therapies Plan in the field of Regenerative Medicine, with funds of €21 million in 2008. This Plan aimed to generate alternative therapies for 12 pathologies without a therapeutic protocol:

- Transplant of pancreatic islets.
- Cell therapy for diabetes complications.
  - Diabetic foot.
  - Diabetic cardiopathy.
- Cell therapy for cardiopathy.
- Cell therapy for Amyotrophic Lateral Sclerosis (ALS).
- Cell therapy for Multiple Sclerosis.
- Skin Regeneration
- Cell therapy of Graft-versus-Host disease.
- Cell therapy for Crohn's disease.
- Regeneration of Bone and Cartilage.
- Cell therapy for medullary lesions.
- Hepatic regeneration.
- Cell therapy for muscular dystrophies.

In 2008, the Carlos III Health Institute (ISCIII), at that time dependent on the Ministry of Health and Consumer Affairs, published a call for award of subsidies[8]. This incorporated a non-commercial clinical research project subprogramme in medicinal products for human use, whose prioritized areas included cell therapy, gene therapy and tissue engineering. In 2009, the ISCIII, now dependent on the Ministry of Science and Innovation published the same call[9], with the difference that the subprogramme of non-commercial clinical research projects with medicinal products for human use, according to article 109.1 of the call, made the opening of the application submission period and the resolution procedure condi-



Notes

8. Resolution of 12 March 2008, of the «Carlos III» Health Institute, publishing the call corresponding to 2008 for the award of financial assistance of the Strategic Action in Health, within the framework of the National R&D&i Plan 2008-2011. BOE (Official State Gazette) of 15 March 2008. BOE (Official State Gazette) of 24 March 2009.

9. Resolution of 20 March 2009, jointly from the State Secretariat for Research and Carlos III Health Institute, publishing the call corresponding to 2009 of the award of financial assistance of the Strategic Action in Health, in the framework of the National R&D&i Plan 2008-2011

tional upon approval of funds which were to be increased by means of a loan budget for the development of this subprogramme. This funding however did not materialise.

Nevertheless, in 2009, the Ministry of Health and Social Policy, through its Directorate-General for Advanced Therapies and Transplants, did publish a call[10] for the award of subsidies to promote the translation of the therapeutic application of medicinal products for human use, orphan drugs and advanced therapies with funding of €16 million.

Furthermore, at the end of 2008, the Ministry of Science and Innovation signed a cooperation agreement with the California Institute for Regenerative Medicine to promote joint initiatives aimed at fostering and accelerating the development of therapies based on stem cell use. One of them consisted of the award of subsidies, within the "Disease Team Research Awards" programme, which encouraged the formation of Hispano-Californian R&D consortia ("Disease Teams") with the purpose of creating international synergies in the translation of stem cell research results from the laboratory through to clinical research. As a consequence of the agreement, a procedure commenced for project selection[11], awarding subsidies subsequently through the call published in June 2009[12], which covered different Subprogrammes of the National R&D Internationalization Programme. This call offered funding for research projects aimed at fostering international cooperation, not just with the CIRM, in the area of translational stem cells research with therapeutic purposes. It also included subsidies for the creation and improvement of infrastructures aimed at fostering international cooperation in the same area, with specific regard to the creation and improvement of clean rooms for the derivation, production, manipulation and use of pluripotent cells for therapeutic purposes.

Notes

10. Order SAS/2481/2009, of 17 September, establishing the call for the award of financial assistance to promote the translation of therapeutic application of medicinal products for human use, orphan drugs and advanced therapies. BOE (Official State Gazette) of 18 September 2009.

11. http://web.micinn.es/05_Investigacion/032CoopIntern/03@Cooperacion/00-PgsInts/web_MedReg_07.pdf

12. Resolution of 26 May 2009, of the State Secretariat for Research, approving the call, for 2009, of the procedure to award financial assistance of several Subprogrammes of the National R&D Internationalization Programme of the National Plan for Scientific Research, Development and Technological Innovation (2008-2011). BOE (Official State Gazette) of 3 June 2009.

Andalusian Overview of Research in Cell Therapy and Regenerative Medicine

The III Andalusian Health Plan 2003-2008 included the development of research in health and healthcare services in its priority lines of action with the objectives of:

- Fostering a culture of excellence in research.
- Boosting existing research resources.
- Identifying the priorities in health research in line with the health needs and problems within the Spanish and European context.
- Fostering research initiatives convergent with projects from the rest of the Spanish Autonomous Regions and the EU with international impact.
- Providing the legal and scientific framework for the performance of research in the cell therapy field.
- Promoting the integration of research, technological development, innovation and evaluation of technologies.

Furthermore, the II Quality Plan of the Andalusian Public Health System 2005-2008 included the research and management strategy of knowledge in Health, incorporating in its lines of action the promotion of collaboration and synergies between basic research and clinical and operational research as well as developing channels of excellence through the consolidation of the Research Institutes in the Health System.

The Andalusian Programme for Cell Therapy and Regenerative Medicine is classified in the framework constituted by the Strategic Plan for Research, Development and Innovation in Health 2006-2010. This Plan aims to establish the foundations of what new translational biomedical research should be in Andalusia as a main source of knowledge, as well as implementing the instruments that facilitate its transformation into innovation. This strategic plan contains within it an operating plan in which a series of lines of action are developed and classified into three areas that aim to reflect the R&D&i production chain in biomedicine: existence of necessary resources, production of quality knowledge and the framework of actions aimed at transferring the knowledge generated to the business sector or to clinical activity. In short, the proposed actions are classified according to:

1. Development of resources

- Public and private finance.
- Human capital: increasing the critical mass, actions to promote talent and the professional development of researchers and research management professionals.
- Structural, relating to both infrastructures and organizational structures.

2. Development of production

- Defining the research framework lines.
- Boosting quality translational research.
- Guaranteeing the integration of research and innovative activity in the objectives of centres and professionals from the Andalusian Public Health System.
- Promoting the development of clinical pharmacological research.
- Incorporating the culture of evaluation of scientific and innovative activity.
- Continuing with the building of a legal framework to guarantee development of research in ethical and safe conditions.

3. Transfer and dissemination of results

- Strengthening the science-technology-enterprise system.
- Legal protection of research results.
- Results transfer.
- Dissemination of results.

The Andalusian Programme for Cell Therapy and Regenerative Medicine, officially created in November 2006, is framed within that context and was drawn up as result of a series of legislative developments and the allocation of financial resources in recent years to develop research projects and infrastructures. One of the factors that promoted its creation was the Declaration of Seville signed, in October 2003, by Bernat Soria Escoms, José López Barneo, Joseph Itskovitz-Eldor, Carlos Alonso Bedate, Francisco Gracia Navarro, Sir Roy Calne, Malcom Alison, Jerònia Lladó, José Becerra Ratia, Marcelo Palacios, Alberto Martínez Serrano and Sebastián Chávez de Diego. This Declaration stated the following:

1. The discovery of stem cells and their therapeutic potential for the treatment of diseases still incurable today is one of the most important advances in biology and medicine in the 20th century.

2. The current state of knowledge justifies investment in basic and applied research on stem cells. Likewise, it is priority to develop new cell lines conveniently characterized and stored in cell banks with free access to the scientific community.

3. Research cannot exclude any of the stem cell types described in accordance with their origin (embryonic, foetal and adult) or of the procedure to generate and obtain them.

4. The exaggerated interpretation of the preliminary data and its dissemination, sometimes striking, may generate unjustified expectations in society that only medium and long-term research can suitably answer.

5. The special characteristics of this area of biomedical research and its potential technological applications demand the cooperation and support of society, the government, social agents and the production sectors in the search for effective public and private funding mechanisms that make it possible to advance our knowledge of basic cell and molecular mechanisms, their therapeutic potential in regenerative medicine and their applications in the development of new drugs.

Furthermore, there has been intense legislative activity in recent years in Andalusia in the field of research in regenerative medicine, to permit a suitable legal framework within which it is possible to perform cell research or the use of therapeutic cloning techniques. As we have already commented, Andalusia was the first autonomous region to bring in legislation regulating research with surplus pre-embryos from fertilization processes to obtain stem cells. Furthermore, it is one of the few regions in the world that now has its own law regulating biomedical research using cell reprogramming techniques for therapeutic purposes, among them that known as nuclear transfer.

In February 2005, three research projects with embryonic stem cells presented by Andalusia to the Ministry of Health were received favourably by the Commission for the Donation and Use of Human Cells and Tissues. The projects were centred on generating insulin-producing pancreatic cells for the treatment of diabetes, regenerative therapy of neurodegenerative diseases and the study of gene expression and cell antigens and embryonic cell lines. In February 2010, there are now a total of 18 scientific studies in embryonic stem cells active in Andalusia approved by the above Commission.

Likewise, the Regional Ministry of Health has directly funded stem cell research projects carried out in the Andalusian public health system as a result of special calls in 2005[13] and 2006[14]. 29 projects were funded to which somewhat more than €2.5 million were allocated. Previously, in 2003, €3.5 million were allocated to direct funding of stem cell research projects, equipment and personnel. Since 2007 [15, 16, 17], the calls for stem cell research projects have been part of the general call of the Regional Ministry of Health, although, in 2008, a specific reserve of €1.8 million was earmarked to prioritize specific cell therapy and nanomedicine projects and, in 2009, close to €2 million were allocated for advanced therapies. More detailed information with respect to research projects and the scientific outcomes of the research is presented in the following chapter of this document, referring not only to stem cell research, but also to genetics and nanomedicine.

Various Andalusian researchers and groups participate in national and international stem cell research networks. The thematic network TERCEL for cooperative Cell Therapy research in the Carlos III Institute, has the participation of 5 Andalusian research groups and the Spanish Society for Gene and Cell Therapy is chaired by Professor José López Barneo. In November 2004 the European Stem Cell Network was constituted in Seville, chaired by Professor Bernat Soria, although this network is no longer active.

The creation of infrastructures at the service of cell therapy and regenerative medicine research has also been a crucial element in the configuration of the Andalusian Programme for Cell Therapy and Regenerative Medicine. Thus, in January 2004, the Cell Line Bank was opened in Granada, forming the seed for the current Andalusian Stem Cell Bank, and in the month of July of that same year, an agreement was signed between the Carlos III Health Institute and the Andalusian Regional Ministry of Health (Junta de Andalucía) in which this bank was constituted as the central node of the National Cell Line Bank and collaboration was established for research in regenerative medicine[18], an agreement which was renewed in 2008[19]. The Bank is responsible for producing, storing, safeguarding and managing the different cell lines, in addition to developing its own research projects. Currently, among the cell lines deposited in this Bank, there are 5 derived from embryonic research in Andalusia: the first three were obtained by researchers from the bank and the two

Notes

13. Announcement publishing the 2005 call for subsidies for research projects with stem cells in the Autonomous Region of Andalusia. BOJA (Official Journal of the Andalusian Regional Government) of 12 December 2005.

14. Announcement published in the national press on 6 November 2006.

15. ORDER of 19 July 2007, establishing the regulatory basis for the award of subsidies for funding research in Biomedicine and in Health Sciences in Andalusia and the calls corresponding to 2007 are made. BOJA (Official Journal of the Andalusian Autonomous Government) of 30 July 2007.

16. RESOLUTION of 7 April 2008, of the General Secretariat for Quality and Modernization, announcing subsidies for the funding of research projects and activities and training stays of research personnel in Biomedicine and Health Sciences in Andalusia. BOJA (Official Journal of the Andalusian Autonomous Government) of 22 April 2008.

17. RESOLUTION of 14 April 2009, of the General Secretariat for Quality and Modernization, announcing subsidies for funding Research in Biomedicine and Health Sciences in Andalusia for 2009. BOJA (Official Journal of the Andalusian Autonomous Government) of 29 April 2009.

18. RESOLUTION of 20 July 2004, of the General Secretariat for Health, publishing the Collaboration Agreement between the Regional Ministry of Health of the Andalusian Government and the Carlos III Health Institute for research in regenerative medicine and implementation of the National Cell Line Bank. BOE (Official State Gazette) of 19 August 2004.

19. RESOLUTION of 6 May 2008, of the General Secretariat for Health, publishing the 2008-2010 Collaboration Agreement between the Regional Ministry of Health of the Andalusian Government and the Carlos III Health Institute, for research in cell therapy and regenerative medicine. BOE (Official State Gazette) of 24 May 2008.

remaining ones were obtained through collaboration between a group of researchers from the Andalusian Centre for Molecular Biology and Regenerative Medicine (CABIMER) and the Hospital Universitario Virgen del Rocío.

In July 2005, the Regional Ministry of Health and the Regional Ministry of Economy, Innovation and Science, the Spanish National Research Council (CSIC) and the Pablo de Olavide and Seville universities, signed an agreement for the creation of CABIMER that opened in March 2006. It has four multidisciplinary departments where cell and molecular biology projects are under development, along with projects for cell signalling, stem cells, and cell therapy and regenerative medicine.

The Andalusian Programme for Cell therapy and Regenerative Medicine is, therefore, configured as a multicentric network of which the Andalusian Stem Cell Bank in Granada, as well as other laboratories and research groups located in different entities distributed throughout Andalusia, form part.

Furthermore, in the last two years, the creation of a network of clean rooms has been promoted that comply with Good Manufacturing Practice (GMP) in research centres, hospitals and regional blood transfusion centres (CRTS) to produce different clinical-quality cell therapies in Andalusian health and research centres intended for use in patients. The location of clean rooms in four tissue banks responds to a strategy the manufacturing of some cell therapy medicinal products included in the National Health System's Services Portfolio[20] under GMP legislation, whilst promoting the development of possible tissue engineering products in our region.

A GMP laboratory has also been built for cell therapy, gene therapy and tissue engineering for mainly training purposes in the Fundación IAVANTE of the Regional Ministry of Health located in Granada. The aim is to develop a pioneering project in Europe to provide training in Advanced Therapies. This programme started in October 2009 and was funding by the Regional Ministry of Health in collaboration with the Ministry of Health and Social Policy. Its purpose is to offer specific training to personnel who are working or who want to work in the field of clinical research and the production of medicinal products in advanced therapies.

Finally, in February 2010, an agreement was signed with Michigan State University allowing Professor José Cibelli to devote part of his time to the management of several research lines to be developed in the Andalusian Cell Programming Laboratory. In this laboratory, presently under construction at the time of preparing this Action Plan, various basic research lines (in the area of the transdifferentiation, dedifferentiation and cell aging) and translational research lines will be developed. This means that this centre will also have a GMP laboratory.

Notes

20. Order SAS/1904/2009, of 8 July, amending appendix III of Royal Decree 1030/2006, of 15 September, establishing the portfolio of common services of the National Health System and the procedure for their updating. BOE (Official State Gazette) of 16 July 2009.

The total number of public GMP rooms are shown in the following table:

CRTS: Regional Blood Transfusion Centre

Centre: CABIMER, Seville
N° production rooms: 2
Status in February 2010:
Certified by the AEMPS (Spanish Agency of Medicines and Medicinal Devices)

Centre: Hospital Universitario Virgen de las Nieves, Granada
N° production rooms: 1
Status in February 2010:
Certified by the AEMPS

Centre: Hospital Universitario Reina Sofía, Córdoba
N° production rooms: 2
Status in February 2010:
Construction finalized. In validation phase

Centre: Hospital Regional Universitario Carlos Haya, Málaga
N° production rooms: 2
Status in February 2010:
Under construction

Centre: Tissue Bank of the Málaga CRTS
N° production rooms: 2
Status in February 2010:
Construction finalized. In validation phase

Centre: Tissue Bank of the Granada CRTS
N° production rooms: 1
Status in February 2010:
Construction finalized. In validation phase

Centre: Tissue Bank of the Seville CRTS
N° production rooms: 1
Status in February 2010:
Construction finalized. In validation phase

Centre: Tissue Bank of the Córdoba CRTS
N° production rooms: 1
Status in February 2010:
Construction finalized. In validation phase

Centre: IAVANTE, Granada
N° production rooms: 1 plus 2 non-GMP culture rooms
Status in February 2010:
Construction finalized. Pilot plant. Training purposes

Centre: Cell Reprogramming Laboratory, Seville
N° production rooms: 3
Status in February 2010:
In design phase

Furthermore, in March 2010, Andalusia already had eight non-commercial clinical trials with adult stem cells authorized by the Spanish Agency of Medicines and Medicinal Products (AEMPS), and four further trials were awaiting authorization by the AEMPS, all phase I-II clinical trials, several of them multicentric, with the participation of not only Andalusian centres. Annex 1 shows the title of these clinical trials and their principal investigators.

Therefore, research in cell therapy and regenerative medicine in Andalusia has received a very important boost in recent years. It is fundamental to promote measures that, in addition to improving the quality and competitiveness of the research, are especially centred on knowledge transfer and on the development of an industrial biotechnological fabric, which will ultimately guarantee that new therapies will reach the general population, whilst also providing a source of wealth for the region.

CLINICAL TRIALS IN ADVANCED THERAPIES 2010	AUTHORISATION´S PENDING	START UP PHASE	RECRUITMENT PHASE	FOLLOW-UP PHASE
CARDIOLOGY:				
Dilated Myocardiopathy			1	
Myocardial Infarction				1
Chronic Ischemic Cardiopathy	1			
NEUROLOGY:				
Multiple Sclerosis			1	
Stroke			1	
IMMUNOLOGY:				
Graft vs Host disease		1		
PERIPHERAL VASCULAR DISEASES:				
Chronic Critical Isquemia in lower limbs in diabetic patients			2	1
Chronic Critical Isquemia in lower limbs in NON-diabetic patients	1	1		
DIGESTIVE				
Hepatic Regeneration	1			

CLINICAL GENETICS AND GENOMIC MEDICINE

Clinical Genetics could be defined as the branch of medicine specialising in the diagnosis and treatment of **hereditary diseases**

Genomic Medicine resolves citizens' health problems by incorporating new knowledge in the human genome and its influence in a great variety of diseases.

At the start of the 21st century, the progress made in the acquisition of knowledge concerning human genetics has drastically changed our understanding of human development and the cause of many diseases. The important conceptual and methodological progress made in this field, culminating in the complete sequencing of the human genome, are making genetics the cornerstone of biomedicine.

The development of DNA analysis technologies and molecular cytogenetics, together with the advance in knowledge derived from obtaining and developing gene maps and the identification of new genes and molecular mechanisms, are opening up new channels for the planning, design and implementation of diagnostic strategies and more efficient therapeutic strategies in genetic based diseases. The diversity of phenotypes related to the changes of a single gene in a large number of genetic disorders, has made the correct handling of clinical variability and genetic heterogeneity key elements in genetic advice, the correct reference for genetic analysis, clinical decision-making and the formation of homogenous cohorts for therapeutic trials. Thus, the evolution of knowledge has, in the last decade, led to a considerable development of the possibilities

for diagnosis and prevention of genetic disorders, and a greater life expectancy and enhanced quality of life for many patients.

Its translation to clinical practice is now making considerable advances possible in the knowledge and clinical handling of "rare disease", in this way achieving greater life expectancy and quality of life in those persons affected. Rare diseases are those pathologies that affect less than 5 individuals per every 10,000 people. 80 % of rare diseases are genetically based. In our neighbouring countries, genetic based rare diseases have a great impact on reproductive safety, and are an important component of perinatal and juvenile morbidity/mortality as well as of adult morbidity/mortality. They also significantly contribute to the incidence and prevalence of congenital anomalies, involve over 5% of the disease load, affect 2% of newborns and represent between 30% and 50% of paediatric admissions.

But genetic research does not only deal with research in rare diseases, generally caused by the mutation of a single gene. It is also enabling a better understanding of the etiopathogeny of common diseases with high social and economic impact, such as diabetes or cancer. Here hereditary factors and the presence of certain specific environmental factors are required in order for the genetic predisposition to become disease.

Genetic diseases, therefore, have significant relevance in terms of public health and care level and with regard to the impact on the quality of life of the people that suffer from them. Furthermore, patients, families and the system additionally bear great social burdens.

The advances in research in Clinical Genetics has not only meant a drastic change in our understanding of human development and of the cause of many genetic based diseases. The translation of the results from biomedical research into clinical practice is promoting new concepts in medicine. This is creating a new scenario leading to greater knowledge of the causes of complex diseases, and bringing us closer to a new paradigm: personalized medicine.

The advances in the genetic mapping of monogenic diseases and the conclusion of the Human Genome Project have generated a great deal of information over recent years. The identification of genes involved in monogenic diseases has enabled the scientific community to consider new therapeutic strategies. Monogenic diseases (e.g. monogenic diabetes, whose prevalence is estimated as close to that of type 1 diabetes, or pigmentary retinosis, the most common form of hereditary blindness) are diseases of great importance, since the definition of the etiology of monogenic diseases opens up the way to a better understanding of the interaction between molecular genetics, human physiology and molecular pathophysiology. Likewise, monogenic diseases significantly help us with the development of personalized medicine.

Gene therapy can be considered as the most direct "genetic medicine" approach. The availability of animal models of human diseases that lead to these pathologies has made it possible to know more about them and will facilitate the development of therapies whose objective is to treat specific genetic diseases. The concept of gene therapy consists of the transfer of therapeutic genetic material to the affected cells to correct or compensate for the altered gene.

Currently, we can highlight the following as being among the lines of research in this field that generate most interest: development of vectors and gene delivery systems with therapeutic orientation, molecular and biochemical analysis of the cell response to gene expression systems, implementation of gene therapy trial protocols and procedures in animal models as well as development of clinical trials based on gene therapy.

In short, after the sequencing of the human genome, research in Clinical Genetics opened up the search for new possibilities for more accurate diagnosis, even at the presymptomatic stage, developing safer and more efficient therapies adapted to population groups with differentiated genetic characteristics, reclassifying some diseases on the basis of their molecular causes and enabling new approaches for epidemiology and public health.

International Overview of Research in Clinical Genetics and Genomic Medicine

When the international public consortium and the project headed by the US company PE Celera Genomics jointly announced in 2000 the first draft of the complete sequence of the human genome, it was the culmination of the Human Genome Project, the great wager taken by the USA. It was sponsored and initially promoted by the Department of Energy at the end of the 1980s and funded with $3,000 million. International contribution and the advance of knowledge in Human Genetics were vital, since they promoted the development of genomic analysis and molecular cytogenic technologies, bioinformatics and access to online information via Internet, together with the advance in knowledge derived from obtaining and developing gene maps and the identification of new genes. Research, development and innovation without which it would not have been possible to complete the Human Genome Project in 2000.

Since then, the USA continues to allocate a large part of public funding to research projects in the field of genetics; indeed, the US NIH, within its 'Roadmap initiative' programme continued to include genomics as one of the key areas among its investment priorities for 2008-2009.

Aware of the impact of this initiatives, Europe committed to research in this field in the 6th Framework Programme (2002-2006), establishing a programme of *Biological, genomic and biotechnology sciences applied to health*. The budget allocated to this Programme was €2,255 million.

In this way, the 6th Framework Programme aimed to integrate postgenomic research within the biomedical and biotechnological approaches for the diagnosis and treatment of rare diseases. Certain aspects of this aim are discussed in the section of the Framework entitled *"Advanced genomics and its applications for health"*. The following sections are also important in this regard: *"Applications of knowledge and technologies in the field of genomics and biotechnology for health"*, given that the research and the development of new diagnostic and therapeutic tools are some of their results, and in particular, the sections headed *"Combating major diseases"*, *"Genomic approaches to medical knowledge and technologies oriented to application"*, and *"Combating rare diseases"*.

In the 7th Framework Programme (2007-2013), Europe has again committed to research in health, placing emphasis on translational research, the development and validation of new therapies, communication of research results, and the establishment of methods to promote health and to prevent and fight against the spread of diseases. It also emphasises the importance of diagnostic instruments and technologies for sustainable and efficient healthcare systems (children's health and demographic ageing). In this case, the budget assigned to this area comes to €6,100 million.

Some of the main international genomic research centres are shown in the following table :

(it does not show Spanish centres as they are shown in the national section)

GERMANY

Berlin

Max Planck Institute for Molecular Genetics

Genetics of development, functional and comparative genomics, bioinformatics, study of neurodegenerative diseases, molecular biology of the metabolism, genomics of cancer, cardiovascular genetics, study of human chromosome 21, study of monogenic diseases, molecular cytogenics and clinical genetics

Jena

Department of Genome Analysis, Institute of Molecular Biotechnology

Detection and functional analysis of genetic and epigenetic variations that determine susceptibility to complex diseases

CHINA

Hong Kong

Genome Research Centre, The University of Hong Kong

Bioinformatics, DNA sequencing, genotyping, transcriptomics, genomic taxonomy. Discovery of new SNPs, studies of structural genomics and of association of complete genomes applied to the study of diseases such as: degenerative diseases, dyslexia, hypertension, osteoporosis, cancer, systemic lupus erythematosus, biliary atresia, schizophrenia and epilepsy.

USA

Cambridge, Massachusetts

Broad Institute of MIT and Harvard
Cancer, genomics, cell signalling routes, clinical and populational genomics, bioinformatics and computational biology.

Boston, Massachusetts

Center for Human Genetic Research, Massachusetts General Hospital
Description of phenotypes, identification of genes causing genetic diseases, diagnosis and gene therapy.

Salt Lake City, Utah

Eccles Institute of Human Genetics, The University of Utah
Genetic expression in prostate cancer; genetic modification in neuropsychiatric disorders, arteriosclerosis, cancer and ageing; bioinformatics; genomics of HIV/AIDS; congenital defects in muscular dystrophy, venous thrombosis and type 2 diabetes; study of homeotic genes; genetic study in neurodegenerative diseases; addiction to tobacco; and study of metabolic diseases and obesity.

Bethesda, Maryland

National Human Genome Research Institute
Identification of genes related to complex diseases and their environmental modifiers; phenotypical studies; improvement of phenotypical analysis strategies in relation to genotypes; study of human genetic diseases to develop better methods for their detection, prevention and treatment; clinical genetics, genetic study of cancer; genomic technology; genome sequencing; bioinformatics

Palo Alto, California

Stanford Human Genome Center
Study of polymorphisms in certain genes causing complex hereditary diseases; search for genes that intervene in arteriosclerosis, Fragile X syndrome, hypertension, Parkinson's disease, autism and resistance to HIV infection; identification of genes causing diseases to contribute to their better diagnosis and treatment.

Houston, Texas

Baylor College of Medicine, Human Genome Sequencing Center
Analysis of human genome sequencing, discovery of functional mutations, clinical genomics

Santa Fe, New Mexico

National Center for Genome Resources
Study of the influence of the genetic variability between the host and pathogen in infectious diseases; bioinformatics; genetic study of cancer; prevention of rare genetic diseases, genetic study of schizophrenia; analysis in human genome sequencing.

Pasadena, California

Center of Excellence in Genomic Science, California Institute of Technology
Analysis of gene expression during embryonic development.

Saint Louis, Missouri

Department of Genetics, Human Genetics Division, Washington University
Genetic analysis of human diseases; studies of evolutionary and morphological genetics; molecular and biochemical biosynthesis of metalloproteins; molecular genetics of neurological diseases such as Alzheimer's and alcohol dependency; predisposition to suffer tumours; genetic study of hereditary diseases; development of genomic technology to treat genetic diseases

Phoenix, Arizona

Translational Genomics Research Institute
Cancer and cellular biology; translational clinical research; computational biology, metabolic and cardiovascular diseases and diabetes; genetic basis of human diseases; integrated genomics of cancer; neurogenomics; genomics of pathogens; pharmacogenomics.

Ann Arbor, Michigan

Center for Gene Therapy (University of Michigan Medical Center)
Production and purification of viral vectors, plasma vectors with marker genes, cytokines, catalogue of recombinant viruses, large-scale production services of recombinant viral vectors, production of transgenic cell lines, etc. Production of transgenic mice; Production of transgenic rats; Production of chimeras in mice stem cells.

Chapel Hill, North Carolina

Gene Therapy Center (University of North Carolina School of Medicine)
Molecular biology of the adeno-associated virus (AAV) to exploit the unique characteristics of this virus to develop an efficient viral vector system, for its use in gene therapy in humans. Facilitating the progression and translation of research in gene therapy from the laboratory to phase I trials for the treatment of human diseases. Two clinical trials that use gene therapy, one to treat Duchenne's muscular dystrophy and the other for Canavan disease.

New York, New York

Department of Gene and Cell Medicine (Mount Sinai Medical Center)
Studies of gene expression, gene regulation, biology of the development and differentiation of stem cells in different tissues, virology, tumour immunology, as well as transplant immunology. Microarrays, live disease models (mice), bioinformatics, molecular modelling, sequencing and genotyping, etc.

Rockville, MD + San Diego, CA

J. Craig Venter Institute
Molecular studies based on the diploid human genome to improve the knowledge of the basis of human health and predisposition to certain diseases. During the next decade this centre will carry out the complete human genome sequencing of individuals, in order to learn more about the genetic basis of diseases (cancer, cardiovascular diseases, respiratory diseases, etc.) through the comparison of the genomic sequences of these individuals.

FRANCE

Paris

Center for the Study of Human Polymorphisms (CEPH)
Identification of genes responsible for susceptibility to diseases; studies of the polymorphism of certain genes.

Evry, Essonne

Genethon
Development of treatments based on gene therapy, rare genetic diseases and neuromuscular diseases.

ISRAEL

Jerusalem

Goldyne Savad Institute of Gene Therapy (Hadassah Medical Center)
Gene and cell therapy, viral and non-viral vectors; development of biotechnological tools and research for gene therapy

UNITED KINGDOM

Manchester

Centre for Integrated Genomic Medical Research (CIGMR)
Genomic epidemiology, phenotypical studies of certain diseases, bioinformatics, DNA sequencing, transcriptomes, discovery of new SNPs, and immunogenetic studies

Edinburgh

MRC HGU - Medical Research Council Human Genetics Unit
Study of the interaction of genes in cancer; structure, evolution, expression and function of homeobox genes in development; molecular genetic studies of mutations; development of a digital atlas and a gene expression database; gene therapy

Oxford

Centre for Human Genetics, University of Oxford
Neurogenetics and genetic psychiatry; genetic study of type 2 diabetes; genetics of cancer; genetics of cardiovascular diseases; statistical and populational genetics; molecular cytogenics and microscopy; genomics and genetic studies of the immune system and inflammation.

Southampton, Hampshire

Division of Human Genetics, University of Southampton (School of Medicine)
Genetic study of cancer; phenotypical characterization of diseases; study of monogenic and chromosomal diseases; research in genetic epidemiology; bioinformatics; study of the genetic mechanisms of disease.

Cambridge

Sanger Institute
Populational and comparative genomics; human evolutionary genomics; dynamic genomics; study of metabolic diseases; molecular cytogenics; genetics of common neurodegenerative diseases; bioinformatics; statistical genetics of diseases; genomics of cardiovascular and neuropsychiatric diseases.

SWEDEN

Stockholm

Gene Therapy Center (Karolinska University Hospital)
Production of plasma vectors of gene therapy under GMP conditions; development of new GMP production technologies on a large scale to meet the centre's demand, as well as new gene transfer system and vectors for gene therapy applications.

TAIWAN

Taipei

Academia Sinica Genomics Research Center
Study of the molecular mechanisms of genes associated to diseases such as cancer or infectious diseases to develop new therapeutic strategies; transferring new discoveries to the pharmaceutical and biotechnological industry.

Spanish Overview of Research in Clinical Genetics and Genomic Medicine

In April 2002, the first call for subsidies for the development of Thematic Networks of Cooperative Research in Health (RETIC) was published, which gave rise to cooperation projects in the field of clinical genetics and rare diseases. The call for creation of Thematic Networks of Cooperative Research through the FIS permitted the creation of two Centre Networks in the thematic area of Genetics: RECGEN and INERGEN. Both networks were developing their objectives and strategic plans, aimed at improving the efficacy of the diagnosis and treatment of the genetic diseases, coordinating and validating the laboratory diagnosis, fostering integrated and translational research, establishing the epidemiology of rare diseases and establishing training programmes.

In 2006, these projects were consolidated through the creation of the Biomedical Network Research Centre on Rare Diseases (CIBERER) by the Carlos III Health Institute, with the objective of fostering excellence in research and the critical mass of researchers in the field of rare diseases, within the INGENIO 2010 programme.

Among other initiatives developed in Spain in this area, we can also highlight the creation of the **Fundación Genoma España** (www.gen-is.org). Its activities include its contribution to implementing initiatives such as the National DNA Bank, the National Genotyping Centre, the National Proteomics Institute, and the National Bioinformatics Institute.

Some of the main national genomic research centres are shown in the following table:

SPAIN

Santiago de Compostela

Department of Pathological Anatomy and Forensic Sciences, University of Santiago de Compostela
Genetics of breast cancer, identification of genes involved in susceptibility to psychiatric disorders, genetic diagnosis of hypertrophic myocardiopathy, studies of genetic factors in patients with hypertension, construction of a DNA chip to diagnose autosomal recessive retinitis pigmentosa and Leber's congenital amaurosis

Barcelona

Department of Experimental Sciences and Health, University of Pompeu Fabra
Study of Williams-Beuren syndrome, study of neuronal diseases, cytogenetics, clinical genetics, bioinformatics, genetics of cancer, epidemiological and populational genetic studies

Centre for Genomic Regulation (CRG)
Identification and characterization of genes and proteins involved in hearing, genetic epidemiology, study of psychiatric diseases, development of molecular tools in neurological diseases and study of genomic variability and susceptibility to diseases, study of genetic factors involved in susceptibility and in pharmacological response to mental diseases.

Madrid

National Oncological Research Centre (CNIO)
Study of polymorphisms involved in breast cancer, search of the BRCAX gene, research on the evolution of populations with the same gene variations associated to cancer, study of genes susceptible to 2 diabetes

Granada

Pfizer-University of Granada-Junta de Andalucía Centre for Genomics and Oncological Research (GENYO)
Human Genetic Variability (study of the genetic basis of diseases such as diabetes, hypertension or degenerative diseases), Pharmacogenetics and Pharmacogenomics, Genomic Oncology

Institute of Biopathology and Regenerative Medicine (IBIMER)
Gene therapy of primary immunodeficiencies, gene therapy of cancer, gene therapy in inmunopathologies.

Seville

Department of Molecular Biology. Andalusian Molecular Biology and Regenerative Medicine Centre (CABIMER)
Genomic Instability / Biogenesis of mRNPs, Epigenetics and expression, integrity and function of chromatin, mitochondrial plasticity and replication, chromosomal segregation

Valencia

Príncipe Felipe Research Centre
Molecular biology of cancer, molecular mechanisms that underlie oncogenesis induced by AIB1, study of mechanisms responsible for neurological alterations in patients with hepatic encephalopathy.

National Genotyping Centre

The National Genotyping Centre is comprised of three nodes, one in the Centre de Regulació Genómica (CRG)-Universitat Pompeu Fabra, another in the University of Santiago de Compostela and another in CNIO. Genotyping of various human diseases, study of genes in cancer

CIBER Rare Diseases

Study of the physiopathology of mitochondrial diseases caused by mutations in the mtDNA, biochemical and genetic-molecular diagnosis of mitochondrial diseases and of metabolic intolerances to exercise, neurogenetics, study of congenital defects and development disorders, clinical genetics and genetic epidemiology, genetic instability and predisposition to cancer.

CIBER Neurodegenerative Diseases

Gene and cell therapy in different neuronal pathologies and Parkinson's disease

Andalusian Overview of Research in Clinical Genetics and Genomic Medicine

Aware of the enormous effects, both present and future, on the health of citizens and for the health organization, advances in these areas may well have, the III Andalusian Health Plan (2003-2008) included as one of its prioritized lines of action *"Integrating the scientific advances of the human genome in research and service provision".*

Strategies for its development include: *"Fostering research in genomics, proteomics and cell therapies, for the comprehensive care of diseases"*, as well as *"Developing specific policies to protect people against possible adverse consequences"* and *"Defining the measures that guarantee protection of citizens"* individual rights: information, right not to know, non-discrimination, confidentiality and informed consent and other ethical considerations, both in health services and in research."

In this line of action, the II Quality Plan of the Andalusian Public Health System 2005-2008 promoted actions aimed at consolidating excellence in biomedical research in Andalusia, through development of new diagnostic and therapeutic options and information management.

Likewise, one of the lines identified in the Strategic Plan for Research, Development and Innovation in Health 2006-2010 is *"to foster the development of excellence in R&D&i regarding prioritized framework lines"*, in harmony with the European Union Framework Programme and the National R&D&i Plan.

This was the context which gave rise to the Andalusian Genetic Plan 2006-2011, the first of this type prepared in our country, following the lines set out in the III Andalusian Health Plan and the other strategic references cited. The Andalusian Genetic Plan pursues the objective of providing quality care for people and families in our community who have genetic based

diseases or are at risk of suffering them, guaranteeing the provision of comprehensive public genetic services, that are multidisciplinary, efficient and harmonized, and which guarantee accessibility and fairness within Andalusian public health system.

The boost provided by the Genetic Plan has enabled Andalusia to be the pioneering region in scientific advances such as **preimplantation genetic diagnosis**, a technique available in the Andalusian Public Health System, by its regulation as a right through Decree 156/2005. Preimplantation genetic diagnosis is applied to embryos obtained by *in vitro* fertilization techniques before being transferred to the uterus, allowing the selection of healthy embryos in couples with a high risk of transmitting a serious hereditary disease to their offspring, thus avoiding the birth of children with serious diseases.

The Genetic Plan includes a set of actions to promote research in **Clinical Genetics and Genomic Medicine**, some of them already embarked on, such as positioning it **as one of the prioritized thematic areas in projects funding** in the 2007 Regional Ministry of Health's call for subsidies for research. It groups these lines of action in different research areas, forming the **Andalusian Programme for Research in Clinical Genetics and Genomic Medicine**, which must be established as one of the main products of the Andalusian Genetic Plan.

Another line of development of the Andalusian Genetic Plan is the recently approved **Andalusian Plan for the Care of People Affected by Rare Diseases 2008-2012**. The development of this plan is directly connected with the Andalusian Programme for Research in Clinical Genetics and Genomic. The rare diseases referred to in this Plan are included in a list which makes it possible to exercise the **right to obtain a second medical opinion**. Since the regulatory recognition of this right by the Andalusian Government, over 700 requests for a second opinion have been processed of which around 30% relate to possible genetically based rare diseases.

Andalusia is also pioneering regulatory legislation in this area. In November 2007, the Andalusian Parliament approved the **Regulatory Act of the Genetic Council, to protect the rights of people undergoing genetic analysis and to protect human DNA banks in Andalusia**, the first regulation to specify the right to genetic advice and predictive medicine, included in the new Statute of Autonomy. A regulatory space was therefore created that enables, with guarantees for the citizen, the detection and prevention of possible hereditary diseases, as well as the conditions for carrying out genetic analysis for healthcare or biomedical research purposes. The legal text also includes the creation of the **Andalusian Public DNA Bank**, which will be set up in the form of a network and whose central node is currently equiping with the resources and infrastructures necessary for its operations.

This central node of the Andalusian Public DNA Bank is located in Granada within the facilities of the **Pfizer-University of Granada-Junta de Andalucía Centre for Genomics and Oncological Research (GENYO)**. It was built thanks to the agreement signed in 2007 between the Regional Ministry of Health and the Regional Ministry of Economy, Innovation and Science with Pfizer and the University of Granada and it's opening is planned for June 2010. This research centre is the first in Spain devoted to genomics, bringing together the government, the University and the biotechnology business and pharmaceutical sector. It puts into practice the agreement established in the Andalusian Genetic Plan for the implementation of facilities that promote exce-

llence in research in the field of human genetic variability, genomic oncology, pharmacogenetics and pharmacogenomics.

One of the lines prioritized by GENYO is **gene therapy** research for cancer. In the field of the gene therapy, Andalusia has research groups currently working on important projects, especially in the areas of gene therapy for primary immunodeficiencies, gene therapy in immunopathologies, gene therapy for cancer and gene therapy for ocular diseases. The research groups leading these projects are particularly concentrated in the provinces of Granada and Seville, located in centres such as the Andalusian Stem Cell Bank, the Hospital Universitario Virgen de las Nieves, the Institute of Biopathology and Regenerative Medicine (IBIMER) of the University of Granada, the Hospital Universitario Virgen del Rocío and the Andalusian Centre for Molecular Biology and Regenerative Medicine (CABIMER).

However, the presentation in June 2000 of the first draft of the complete sequence of the human genome can be considered as the end of the start of the new scenario promoting new concepts in Medicine. It is reasonable to expect that as our knowledge progresses on the human genome and its relation to health, susceptibility to disease and response to treatment, we will have a fuller understanding of the basic mechanisms of life that brings us closer to the ambitions formulated by Osler.

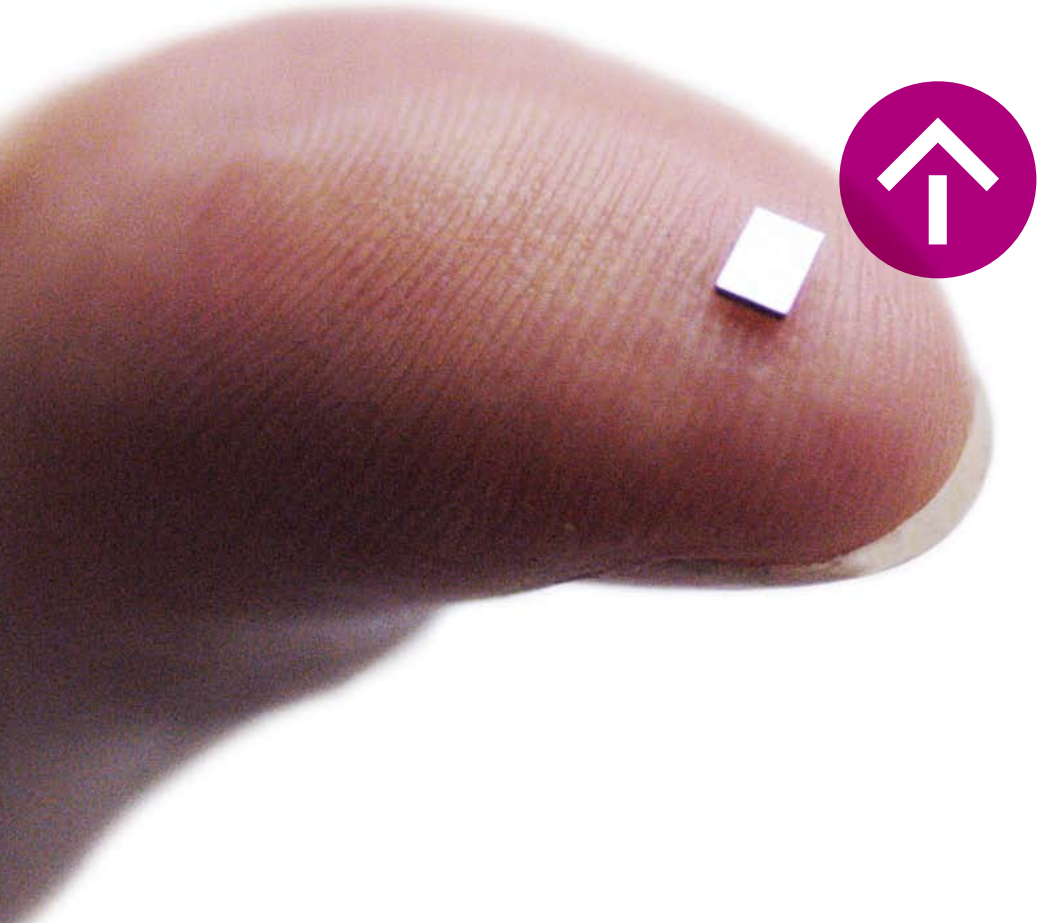
Finally, in September 2009, the Regional Ministry of Health presented the **Medical Genome Project** (PGM). The initial budget of the PGM came to €27 million, and its objective is the preparation of a reference standard for the human genome and the identification of genes responsible for genetic based diseases. Therefore, Andalusia will have one of the largest high-performance sequencing platforms in Europe. The reference standard will be obtained from the megasequencing of DNA samples from 300 phenotyped controls. The comparison between the genomic reference sequence and the genomic sequences of patients will allow the identification of a significant number of new genes responsible for rare diseases within a short period of time, contributing to the improvement in their diagnosis, prevention and treatment.

We can predict advances in biomedical research, the development of pharmacogenetics and pharmacogenomics and their potential capacity to provide individualized therapies, the availability of information that allows us to anticipate the risk of developing certain diseases and to determine the most effective preventive measures, although this information is still far from systematic diagnostic and therapeutic applications. In any case, this should not surprise us since the timeframe for the development of new pharmaceutical products is over 10 years. However, we are all aware that it will be research, innovation and development that, through the safe, efficient and sustainable transfer of new knowledge to clinical practice and the provision of health services, will contribute to a greater life expectancy and better quality of life for Andalusian citizens.

To that end, the **Andalusian Programme for Research in Clinical Genetics and Genomic Medicine aims** to carry out the pertinent actions in these areas of knowledge with a clear health orientation and with the aim of supporting research work within the Andalusian Public Health System. The programme must also contribute to making us competitive with our other European partners and favour national and international alliances.

NANOMEDICINE

The **nanomedicine** aims, by the development and application of nanotechnology, to improve the diagnosis, treatment and prevention of diseases and traumatic lesions, as well as preserving and improving patients' health and quality of life



Nanotechnology is increasingly linked to advances in biotechnology and information technologies and may potentially be one of the most innovative disciplines of the 21st century. All forecasts indicate that this will be a key technology in many sectors, especially relevant in medicine, specifically in the development of new treatments, both preventive and therapeutic, as well as of new diagnostic and drug dispensing methods. In the not very distant future, nanotechnology will be fundamental to the tools available making treatments possible which are specific to each patient's requirements.

The Nobel Prize physicist, *Richard Feynman*, with his famous phrase "There's Plenty of Room at the Bottom" was the first to refer to the possibilities of nanoscience and nanotechnology in the speech he gave in Caltech on 29 December 1959. Feynman had the innovative vision that, just as nature creates different structures starting from the same type of atoms, it would be possible to design and synthesize different materials and structures from the reorganization of atoms and molecules in line with human interests. Over the years, this vision was supported by other scientists such as *Erick Drexler*, who predicted that nanotechnology could be used to resolve many of the problems of humanity in three very sensitive areas for our future as a species: health, management of energy resources and the capacity for processing large volumes of information. However, it was not until the start of the nineties that the boom in this new discipline took place and scientists started to design and create nanometric structures through the manipulation of basic natural elements such as atoms and molecules. Scientists' interests in these new structures is due to the properties they have because of their nanometric scale dimensions. The properties of

these materials, very different to their corresponding ones in volumetric state, are demonstrating their use, presenting innovative solutions in countless fields from electronic engineering to biomedicine.

Nanomedicine, therefore, can be defined as the application of nanotechnology to health. It is an interdisciplinary field of scientific and technological research that aims, by the development and application of nanotechnology, to improve the diagnosis, treatment and prevention of diseases and traumatic lesions, as well as preserving and improving patients' health and quality of life.

With this view in mind, nanomedicine opens up a new avenue in the fight against disease with high socio-economic impact, such as cancer, cardiovascular diseases, neurodegenerative diseases (Parkinson's, Alzheimer's), arthritis, diabetes and infectious diseases. Furthermore, nanomedicine could be one of the most competitive disciplines in contributing to the sustainable progress of the Third World, providing new methods of diagnosis and screening of diseases, better systems for drug administration and tools for monitoring some biological parameters with a very significant final cost reduction.

The fundamental characteristic of nanomedicine is that it constitutes an interdisciplinary assembly of different fields such as physics, chemistry or medicine, in which each field contributes in some fundamental aspect. Therefore, this discipline cannot be performed with a vertical approach, rather it is necessary to take a horizontal view of its combination with other sciences such as chemistry, biochemistry, molecular biology, physics, pharmacy, toxicology, IT, bioengineering and materials sciences. The multidisciplinary approach needed by nanotechnology means that it requires a special impetus with regard to training materials, these being particularly necessary in inflexible educational environments.

Certainly, nanomedicine will be one of the key tools in healthcare model change, where it will be possible to control and improve patient heath depending on their predispositions, to diagnose disease in presymptomatic state, to administer drugs aimed at therapeutic targets with extremely high specificity and to use image-based non-invasive tools to verify the efficacy of the treatments in progress.

In this regard, the research context of the Andalusian Public Health System, meets the optimum conditions to develop the translational research that is so necessary in this field. It can offer direct solutions to citizens, promoting the execution of applied research programmes, carrying out clinical trials in this field and developing patents with real commercial potential.

International Overview of Research in Nanomedicine

It is well known that the growth in research activity in nanomedicine in the last decade has grown considerably, both qualitatively and quantitatively. The number of publications in this discipline has gone from 10 articles in 1980 to over 4,200 articles in 2007. Some countries already allocate large resources to nanotechnology research, in order to be at the cutting edge in nanomedicine research at a global level. Of these countries, the USA is in the lead with 32% of publications and 54% of valid patents. A long way back we have countries such as Germany (with 8% of publications and 12% of patents) and Japan (9% of publications and 5% of patents). United States leads, furthermore, in terms of the financial return generated by research in nanotechnology, which has proven itself to be profitable in economic terms for the entire country's productivity over the last five years.

The following table shows the most outstanding international research centres for their research in nanomedicine

(it does not include Spanish centres as they are shown in the national overview).

GERMANY

Muenster

Center for Nanotechnology, (CeNTech)
Synthesis of nanostructures, study of their mechanical properties, nanostructure-biomolecule interaction. Analysis of cell behaviour using nanotechnology tools.

Berlin

Center of Biomedical Nanotechnology
Development of fluorescence resonance energy transfer (FRET). Development of lab-on-a-chip. Nanobiosensors.

St. Ingbert

Fraunhofer Institute for Biomedical Engineering
Development of nanotechnology techniques and approaches for diagnosis.

Munich

Center of Nanoscience (CeNS)
Synthesis, characterization and modification of the surface of nanostructures with electrical, mechanical and optical properties. Biological applications with nanostructures. Development, optimization and biological application of the AFM technique.

In part, these centres have served as a source of information regarding the strategies implemented to increase the generation of health-oriented nanobiotechnology knowledge. We have summed up their fields of development in words and key phrases with the idea of highlighting where special emphasis should be placed in relation to knowledge generation.

AUSTRALIA

Melbourne, Victoria

Centre for Nanoscience and Nanotechnology (CNST), University of Melbourne
Development of nanostructures for drug delivery. Studies of the surface modification of nanostructures for their application as biosensors. Development of nanostructured surfaces for tissue engineering.

CANADA

Edmonton

National Institute for Nanotechnology (NINT)
Synthesis and characterization of nanocrystals and nanowires. Manufacturing and characterization of nanosensors. Development of nanomaterials for catalysis. Development of nanoelectromechanical systems (NEMS).

Ottawa

Steacie Institute of Molecular Science (SIMS)
Development of nanobiosensors for genomics and proteomics.

Vancouver

The Advanced Materials and Process Engineering Laboratory (AMPEL)
Quantum coherence in nanostructures. Molecular nanoscience and engineering.

USA

Purdue

Birck Nanotechnology Center
Nanophotonics. Nanoelectronics. Nanomechanics. Development of electronic nanobiosensors for proteomics and genomics. Development of NEMS for clinical applications.

Santa Barbara and Los Angeles

California Nanosystems Institute at UCLA and UCSB
Development of Nanobiosensors for cancer detection. Nanovehicles and nanostructures for drug delivery.

Baltimore, Maryland

Institute for NanoBioTechnology at Johns Hopkins University
Research in cell and molecular dynamics through nanotechnology techniques. Development of nanodevices for diagnosis and drug delivery. Study of the impact of nanotechnology on health and the environment.

California

The Kavli Nanoscience Institute (KNI CALTECH)
Study of the optical and electrical properties of semiconductor nanostructures. Development and manufacturing of NEMS.

Ithaca, NY

Nanobiotechnology Center, Cornell University
Manufacturing of nanostructures for detection, separation and analysis of molecules and surface-cell interaction studies.

Cambridge, Massachusetts

Massachusetts Institute of Technology
Research in nanoengineering, nanostructures and nanobiotechnology

Center for Nanoscale Systems, Harvard University
Development of components on a nanoscale that can be integrated in large and complex interaction systems.

Indiana

The Notre Dame Center for Nano Science and Technology (NDnano)
"Top-down" synthesis and characterization of nanostructures. Study of the interaction between nanostructures and biomolecules or organisms.

Houston, Texas

Center for Biological and Environmental Nanotechnology, (CBEN)
Development of nanodevices for drug delivery in tumours. Synthesis of infrared visible nanoparticles for contrast agents. Manufacturing of nanoparticles for hyperthermia treatments.

Chicago, Illinois

Institute for Bionanotechnology in Medicine (IBNAM)
Development of nanostructured scaffolds for tissue engineering. Manufacturing of nanobiosensors for genomics and intelligent drug delivery nanosystems.

Servicio Andaluz de Salud. Consejería de Salud. Junta de Andalucía.

FRANCE

Villeurbanne

CNRS
Nanostructures for the development of biomimetic systems.

Paris

French National Institute for Health and Medical Research (INSERM)
Development of Micro and nano-tools for applications in diagnosis and treatment.

Grenoble

Rhône-Alpes Center in Nanoscience
Nanoelectronics, nanomagnetism, nanophotonics, nanochemistry and nanobiosciences, nanomechanics and microfluidics

Montpellier

Central Technology in Micro and Nanoelectronics, University of Montpellier II
Nanoelectronics, nanostructures and nanomaterials

ITALY

Modena

National Center for Nanostructures and Biosystems at Surfaces (S3 CNR-INFM)
Manufacturing of nanostructures and nanobiosystems. Studies of the nanometric surface/interface phenomenon. Nanosimulation.

Lecce

National Nanotechnology Laboratory. Lecce
Synthesis, characterization and modification of nanostructure surfaces. Applications in diagnosis.

NETHERLANDS

Delft

The Kavli Institute of Nanoscience, Delft University
Study of the molecular dynamics of the cell using nanotechnology approaches. Development of nanodevices for molecular detection.

UNITED KINGDOM

Cambridge

Cambridge Nanoscience Centre, University of Cambridge
Synthesis and characterization of nanotubes and other nanostructures. Study of their chemical and electrical properties. Study of nanostructure-cell interaction. Applications of nanostructures for molecular imaging.

Glasgow

James Watt Nanofabrication Centre, Glasgow University
Micro and nanofabrication. Lab-on-a-chip.

London

The London Centre for Nanotechnology, (LCN)
Development of nanosystems for detection of molecular processes for disease diagnosis.

Oxford

The Bionanotechnology Interdisciplinary Research Collaboration (IRC)
Synthesis, manufacturing and self- assembly of nanostructures. Development of electronic biosensors.

SWEDEN

Lund

Lund University
Synthesis and development of nanostructures for manipulating and analysing individual cells.

In order to assure that it can be competitive in nanomedicine research, Europe has strongly committed to this new discipline in the 7th Framework Programme (2007-2013), which establishes nanotechnology as a thematic priority. In fact, Nano2Life (N2L) had already been constituted in the 6th Framework Programme (2002-2006), as the first European Network of Excellence in nanobiotechnology, with the objective of supporting European efforts to be a first-rate player in this field, with special attention to knowledge transfer between the interested groups, companies and European institutions. In the 7th Framework Programme 2007-2013, nanosciences and nanotechnologies reappear again as thematic priorities.

The lines of action that must be enhanced in our Autonomous Region to be aligned with available funding instruments are:

a) New imaging agents, necessary for detecting a disease or cellular malfunction in the earliest possible stages, both *in vivo* and *in vitro*. Nanotechnology applications are demonstrating themselves to be very promising in *in vitro* studies, however, a special effort is necessary in *in vivo* approaches. It is in this latter case where there is a need for greater knowledge and an optimum transfer potential.

b) Drug delivery systems or therapeutic nanosystems, to transport and deliver drugs, in controlled manner, to affected areas, thus achieving a more effective treatment, that is less costly and with fewer secondary effects.

c) New nanostructured materials capable of modifying cell behaviour and inducing tissue regeneration, to repair and reconstruct damaged tissues and organs, the tendency moving from tissue engineering *in vitro* to tissue engineering *in situ*.

d) Development of "Lab-on-a-chip" useful for performing different diagnostic tests at the same time.

In the literature, there is little information on the performance of international clinical trials and indexed databases have not yet incorporated this specific term in their thesaurus due to the recent incorporation of this discipline as a research priority. However, we can get an idea of the results obtained by this type of studies through patent application data. Different countries have registered 4,675 patents related to nanostructures in the international databases as well as 231 patents in relation to nanodevices, both for disease diagnosis[21].

At present, efforts to market nanomedicine applications are much more marked in the USA, which is leading this process with 50% of the companies involved in developing this discipline compared to Europe's 35%.

Notes

21. European Patent Office database.

Spanish Overview of Research in Nanomedicine

At a national level, among the initiatives promoted in Spain after 2000 we can highlight the creation of wide spectrum thematic networks, of multidisciplinary character, which have enabled the interrelation of scientific communities unconnected until that point, encouraging interaction between Spanish groups. The Nanociencia and NanoSpain networks constitute the two clearest examples of self-organizations of scientists. The *Nanociencia network*, which is no longer active after being in existence for four years, was pioneering in the Spanish field. It contributed to training through the sharing of methodologies, gathering together almost two hundred researchers. On the other hand, *NanoSpain* was configured as a much bigger network (it currently comprises almost 180 research groups from public and private sectors) with the clear intention of promoting the existence of a new type of knowledge, necessary for achieving the generation of competitive science and fostering a new technological and economic revolution involving the authorities, scientific managers and the general population. Another initiative, promoted by the Fundación Phantoms, is the series of conferences called *"Trends in Nanotechnology"* and *"NanoSpain"*, which have been held across Spain annually since 2000 and act as an international benchmark. These gatherings, a real showcase of Spanish research, have managed to attract highly reputed international researchers in nanotechnology, fostering a strong interaction

Servicio Andaluz de Salud. Consejería de Salud. Junta de Andalucía.

with Spanish groups. These initiatives, although successful, need to be maintained and encouraged to strengthen the position of Spanish groups with respect to foreign groups and achieve their full integration in the European Research Space.

At the start of 2003, nanotechnology initiatives began to multiply and their joint impetus was consolidated with the emergence of the National R&D&i Plan 2004-2007, where nanotechnology found its niche, being incorporated as a main objective in many of the National Programmes and adopting a prominent role for itself in its own right through the Ministry of Education and Science (MEC) Strategic Action on Nanoscience and Nanotechnology. In this call (the only call in 2004), a third of the projects approved were focussed on the study or development of nanotechnologies applied to biomedicine.

However, it was not until 2005 when the support of the Spanish state for nanomedicine became much more palpable with the implementation of the INGENIO 2010 programme. This programme is dedicated solely to the support of the development of nanomedicine in Spain, with three programmes or actions promoted by the three Ministries involved:

CONSOLIDER PROGRAMME

MINISTRY OF EDUCATION AND SCIENCE

The NANOBIOMED programme "Nanotechnologies in biomedicine" is one of the 17 projects selected in the first CONSOLIDER call of the Ingenio 2010 programme (2005 call) with the objective of favouring excellence in research and technology transfer in our country. The NANOBIOMED project combines the experience of relevant scientists in different areas of research (physics, chemistry, biochemistry, pharmacy and medicine) in an attempt to prevent and cure diseases through the use of nanotechnology. The project's objectives are centred on the application of nanoparticles in two important areas: nanotherapy and nanodiagnosis. The research proposed has been developed in close connection with industrial partners, who are already collaborating with the different research groups in certain projects or who have shown interest in these research lines.

The NANOGUNE project was selected in the 2006 call. Nanogune initially had fifty elite scientists selected for the excellence of their research, to whom we have to add a larger number of researchers, coming from universities and from other groups, who will become part of a network. Nanogune has five laboratories equipped with cutting edge technology to perform research into advanced microscopy, nanosystem simulation, nanostructure assembly and characterization of atomic-scale materials.

CENIT
PROGRAMME

MINISTRY OF INDUSTRY, TOURISM AND TRADE

This programme provides subsidies allocated to promoting stable public-private cooperation in research, development and innovation in areas of strategic importance for the economy, by creating national strategic consortia for technical research.

Of the 16 subsidies awarded in 2006, 2 corresponded to nanotechnology projects applied to biomedicine: OCNOSIS and NANOFARMA.

OCNOSIS' goal is to develop new and improved tests to detect the early development of oncology disease, thus increasing the probability of its cure. It also aims to develop strategies for treating this disease, based on the knowledge of the changes that characterize cancer cells. NANOFARMA is a multidisciplinary project with the aim of innovating and developing nanotechnology platforms in the field of Drug Delivery Systems (DDS).

CREATION OF THE
CIBER
Bioengineering, Biomaterials and Nanomedicine

ISCIII
MINISTRY OF HEALTH AND CONSUMER AFFAIRS

The Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), funded by the Carlos III Health Institute, was established in March 2007 with the objective of coordinating and amalgamating the forces of the main research centres, universities, industry and hospitals in the sector. The centre's research focuses on two main areas: firstly, the development of systems to prevent, diagnose and monitor and secondly, technologies related to specific therapies such as Regenerative Medicine and Nanotherapies.

In the new National R&D&i Plan 2008-2011, nanoscience and nanotechnology re-emerge as priority lines of research, showing the support that the Spanish government continues to place in this field.

As a result of this whole strategy, aside from the increased impact of knowledge dissemination through scientific publications, 189 patents have been generated in Spain related to nanostructures for dispensing medicinal products and 4 patents related to nanodevices for the diagnosis of health problems. These figures are in line with the international level of patents developed for treatment and those for diagnosis of health problems.

Some of the most outstanding Spanish nanomedicine research centres are shown below:

SPAIN

Zaragoza

Institute of Nanosciences, UZ Aragon
Nanomagnetism. Nanometric and nanomolecular materials. Nanoporous membranes and catalysis. Functional organic materials.

Barcelona

Catalonia Institut of Nanothecnology. Nanoscience and Nanotechnology Research Centre (ICN-CSIC). CIN2
Synthesis and characterization of inorganic nanoparticles, and studies on nanoparticle-biomolecule interaction.

Institute for Bioengineering of Catalonia (IBEC)
Biolectric characterization on a nanoscale. Bionanophotonics of individual molecules. Nanobioengineering to obtain new intelligent subsystems.

San Sebastián

Centre for Cooperative Research in Nanosciences (NanoGUNE)
Synthesis of nanosurfaces by lithographic and layer-deposition techniques. Manufacturing and development of electronic nanodevices and nanodevices with infrared optical properties.

Centre for Cooperative Research in Biomaterials (BiomaGUNE)
Contrast agents for the optimization of MRI and PET techniques for molecular imaging. Research on the nanoparticle-cell interaction for development of new diagnosis and therapy techniques.

Andalusian Overview of Research in Nanomedicine

On a regional level, and in accordance with the priority lines of national research, Andalusia is committed to research in nanotechnology, especially in nanomedicine.

Therefore, the Regional Ministry of Health and the Regional Ministry of Economy, Innovation and Science, together with the University of Malaga, have joined together to implement the Andalusian Centre for Nanomedicine and Biotechnology (BIONAND); a centre where researchers from the university, business and healthcare fields work in order to generate knowledge and innovation in the nanomedicine area.

BIONAND aims for excellence in research in various areas of nanomedicine with clear future opportunities. Together with the work carried out in Andalusia's benchmark centres Cell Therapy and Regenerative Medicine (CABIMER, in Seville) and Clinical Genetics and Genomic Medicine (GENYO, in Granada), as well as other health research centres, a solid and competitive platform is being created for the specialization of the Autonomous Region of Andalusia in research into new systems in the fight against disease.

In the current overview of research in nanomedicine in Spain, BIONAND will be the country's first thematic centre in nanomedicine and nanobiotechnology applied to health. Although there are already nanotechnology centres in Spain including different disciplines, as of today there is no centre in Spain exclusively devoted to nanotechnology research applied exclusively to health. The central philosophy, including the set of activities that will be carried out in the centre, can be summarized as follows:

a) Generation of knowledge, using nanotechnology tools and approaches, making it possible to understand biological mechanisms which are central to the physiopathology of those diseases which have been prioritized in the plans and strategies of the Regional Ministry of Health.

b) Research aimed at a better understanding of the emerging properties and characteristics of materials on a nanometric scale, leading to the development of nanotechnology-based biomedical applications.

Therefore, in order to maximize the centre's level of competitiveness and with its aim in mind of becoming a benchmark centre, BIONAND has set out its objective to focus its research guidelines on nanostructured systems with health applications, including both simple structures (nanoparticles, nanotubes and other nanoforms) and more complex structures (micelles, liposomes, polymeric capsules, dendrimers...). This specialized vision of the centre aims to optimize the concentration of equipment and human resources, in an area which demands high competency levels. This factor sets BIONAND apart with respect to other centres in its milieu.

RESULTS TRANSFER

During the last thirty years both the USA and Europe have concentrated their efforts on developing their innovation models, transforming them into systems which **make greater use of resources** allocated to research

Initially, innovation systems or models were based on what was called *"Open Science Models"*, immediately disclosing the research results, without having previously "packaged" those results (e.g. patents, utility models, etc.) with the corresponding industrial property rights (IP) for their suitable transfer.

Little by little, the science model evolved towards a new innovation model, the *"Licencing Model"*, with active participation of industrial property rights to protect the research results. In this model, after the industrial property rights were generated, they were transferred to companies in exchange for a payment to the Public Research Bodies (PRB) that generated the knowledge.

In recent years, Europe has wanted to take a further step forward and has become more proactive in the value generation processes, utilising the research carried out by the PRB, with the support of a new transfer model. This model, known as the *"Innovation Model"*, which should not be viewed as a conflicting with the licencing model, aims to increase collaboration between the PRB and Industry, as well as promoting greater involvement of the former in generating spin-off companies. With this in mind, the different EU governments have endeavoured to create subsidy programmes to promote public-private collaboration and encourage this new

model. The member countries have also supported the system by setting up legal bodies as important as those of Offices of Technology Transfer (OTT) and establishing their own subsidy programmes for generating spin-off companies and public-private collaboration.

In the specific case of Spain, and more specifically in the case of Andalusia, the measures adopted to date have enabled a great increase in relative terms in the number of collaboration agreements signed with the private sector, in patent applications filed and in spin-offs. However, when we compare concrete data with our neighbouring countries, the outlook is not as encouraging.

According to the Department of Statistics of the European Patent Office, in 2007 Spanish applicants applied for 1,283 European patents, a number representing approximately a quarter of the patents applied for by Italians, an eighth of those applied for by the French and a twenty-fifth part of those applied for by Germans. In Andalusia, the number of patent applications increased in the 1999-2008 period by over 100%, being the third most active Autonomous Region in this area without taking the size of the population into account. If we adjust the weighting accordingly, Andalusia is in fourteenth position behind regions such as Asturias or Murcia. If we also bear in mind that many applications do not come from PRB, but are filed by individuals and companies, it seems clear that greater effort must be made in research protection work, since this situation, although endemic in Spain, is much more marked in Andalusia, despite the funding effort made by the State and the Andalusian Government, with a significant growth in expenditure on R&D in recent years.

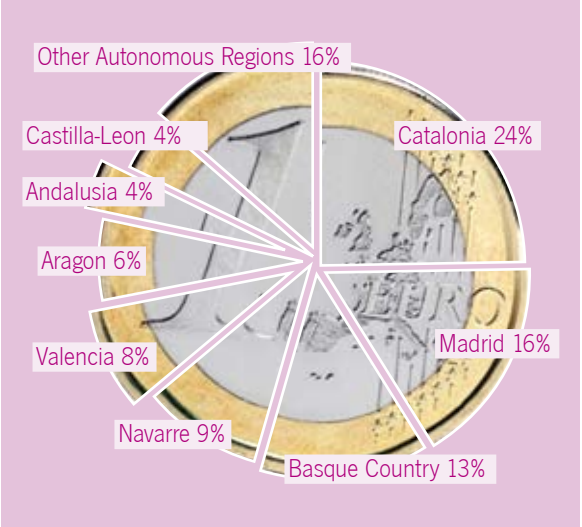
As regards state public-private collaboration, the growth in the volume of funds contracted in the 1996-2006 period increased from €122.2 million to €428 million. According to the RedOtri 2006 report, this increase was mainly motivated by the CENIT programme from the Centre for the Development of Industrial Technology (CDTI-Ministry of Industry) which was specifically set up to promote these types of collaborative initiatives. However, from the total sum of subsidies provided by the Ministry through the CDTI, only 4% were allocated to Andalusian companies and PRB in 2006. Investment was spread across the following areas :

1. Agrifood and environmental technologies.
2. Information and communications technologies (ICT).
3. Production technologies in chemical, health and materials technology.

Other regions such as the Basque Country and Navarre, with a much lower population than Andalusia, attracted 13% and 9% respectively of the investment in CDTI[22] subsidies.

Distribution of CENIT's total budget by region

Source: CDTI. 2006 Annual Report.



Notes

22.CDTI, Annual Report 2006.

This failure to attract public resources is directly due to the low-level industrial fabric base in Andalusia where little technology has yet been introduced. Andalusia, thus, has little capacity to attract subsidies specifically allocated to promoting technological development via collaboration agreements. Probably, one of the most inadequate areas in this regard is that formed by companies involved in health sciences and biotechnology. This means that the research results transfer in these areas is incredibly complicated, simply as there is a lack of suitable, interested parties in the region, since physical proximity to the PRB is a determining factor when reaching transfer agreements.

The undeveloped industrial fabric of Andalusia is not only characteristic of the Andalusian manufacturing system, but is also typical of Spain as a whole. Together with low patent production, these two factors can be considered as two of the main causes of the low revenue figures from royalties and contracts obtained by the PRB. According to a survey published by RedOtri for 44 Spanish universities, the revenue arising from royalties received by Spanish universities only amounted to €1.97 million in 2007[23].

This brief review highlights different factors greatly affecting the value generation chain that spans knowledge generation to its transfer into the "Licencing model" and "Innovation model" discussed above. For this reason, new methods should be established or alternatively adapted to support the existing methods in order to foster the generation of industrial property assets, encourage public-private collaboration and encourage the creation of a more favourable industrial fabric into which the technologies or know-how can be transferred.

Generation of industrial property assets

Boosting the generation of industrial property assets is not an end in itself but is vital in helping to achieve suitable transfer of knowledge . The translation of technology from knowledge management can be carried out through various channels, two of which are set out below:

1. Licencing or assigning that knowledge to an entity capable of maximising returns on it
2. Creating the industrial fabric based on this knowledge (*spin off, NEBT, etc.*)

The licencing/assignment process, as well as the company generation process, involves a great amount of resources, time and effort, hence the importance of guaranteeing that the technology or the products from R&D&i results are correctly protected, that the risks of infringement are reduced to a minimum, if not completely overcome, and that legal security is maximised.

Notes

23. RedOTRI, Annual report 2008.

Servicio Andaluz de Salud. Consejería de Salud. Junta de Andalucía.

Some years ago in Spain, plans were implemented to promote technology transfer and there has been an increase in resources to fund research which must fuel the transfer process. One of the key bodies in these plans has been the Offices of Technology Transfer who have been tasked with the plans to promote industrial property rights, with the management in the broadest sense of these plans and advising on the processing of public subsidies (regional, national and EU).

The creation of European Project Offices, generally established within the OTT, has been another of the initiatives taken to stimulate participation of PRB in research activities funded by the European Union (EU).

In the specific case of OTT, although the work they are doing with the Spanish innovation model is considered very positively by the industry, their efforts to efficiently promote knowledge transfer are considered insufficient.

The technology watch that itself involves the arduous and tedious work of searching for and analysing *technology offers* that are in line with the needs of each company, becomes even more complicated when the response received from the technology demands by the OTT is very low and, in those cases when responses are received, it is provided in the form of very unstructured information. Furthermore, it may happen that after making these first contacts, few offers are subsequently received as a result of the OTT's initiative. Thus, there is no ongoing OTT-Industry dialogue and where it does exist is generally limited to very sporadic contacts, typically initiated by the companies.

Another particularly relevant and very well known fact, but one which continues to damage the transfer process, is the prevalence of continuous publications with protectable inventions that all too frequently occur in Spanish PRB. This continued loss of value is not due, in most cases, to a passive attitude of researchers to the innovation system, but is caused by the total ignorance regarding what can or cannot be patented. This loss of opportunities is the direct responsibility of the researchers and the OTT who must make sure these circumstances do not arise.

As stated by the OTT specialists, both the lack of control of the OTT over the research carried out by the PRB research groups, and their backwardness in making technology offers, are due to the lack of resources to recruit staff to promote and market the offers and the excessive number of research groups to monitor. This situation, in addition to the aforementioned consequences, causes delays in processing the patents and this discourages researchers from devoting part of their research work time to a job that, on occasions, they consider something secondary or even outside the scope of their work.

On the other hand, although usually overlooked in the transfer process and especially in the licencing process, the researcher plays an extraordinarily key role in its satisfactory conclusion, with their direct involvement in the technology marketing phase. According to an article published by the NIH[24] on a study involving 281 licensing agreements signed between 2001 and 2004, 38% were established as a result of the researcher's contacts and the remaining 62 % were due to the marketing work carried out by the OTT and the public information available *(see charts)*.

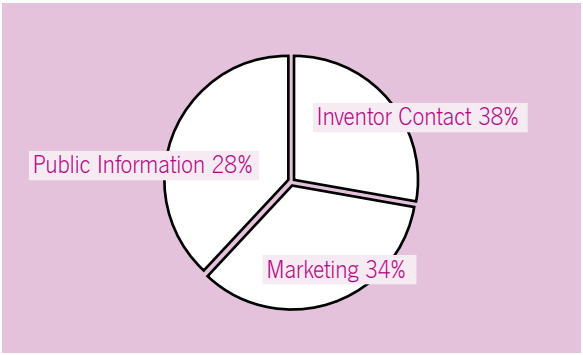
Generally, the involvement required of researchers in the transfer process is extremely difficult to combine with their teaching activity, research and, especially in the case of hospitals, with the public and private execution of their medical work. This workload is increased by the bureaucratic effort demanded for researchers to apply for and justify the subsidies to fund their research.

Notes

24 NIH V. Ramakrishnan, et al. 2005

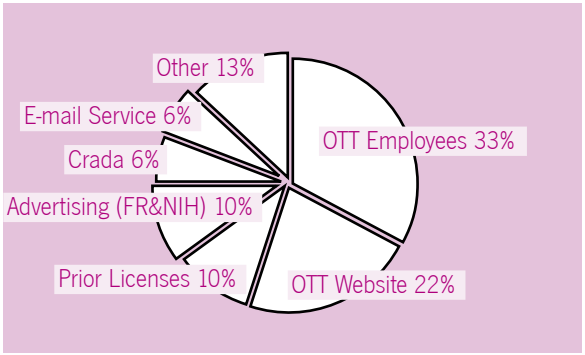
Origin of licence holders
(study of 281 licences 2001-2004)

Source: NIH V. Ramakrishnan, et al. 2005



Role of marketing in the transfer process
(study of 281 licences 2001-2004)

Source: NIH V. Ramakrishnan, et al. 2005



Promotion of public-private collaboration

Although the indices of collaboration between PRB and companies are the transfer indicators that show the most favourable progress in our country, this must be one of the aspects of the transfer system to which the most commitment should be made, since in itself it promotes the alignment of scientific-technology supply with business demand. This is one of the great failures of the innovation system and produces a clear waste of the resources allocated to research.

Servicio Andaluz de Salud. Consejería de Salud. Junta de Andalucía.

Notes

25. Lambert Report 2003.
26 OCDE, Report Turning Science into Business, 2003.

Maximization of the use of these resources, together with the alignment of technology supply to business demand must be one of the core elements of research support policies, nevertheless without at any time sidelining the Open Science Model. The PRB must understand they are one of the main and essential engines of the innovation system without forgetting that their main mission is the generation, disclosure and transfer of knowledge.

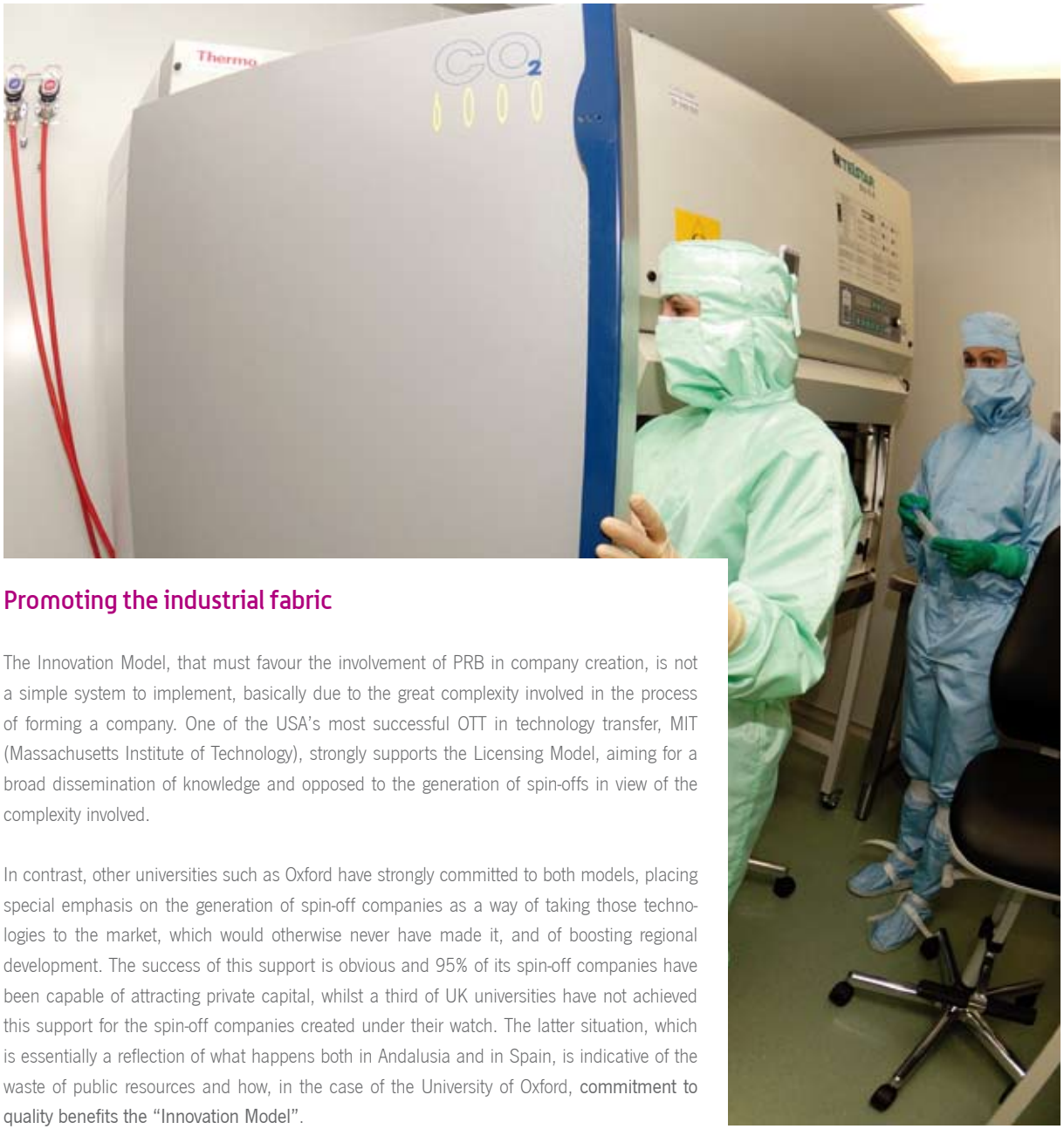
Research carried out as a result of collaboration is usually largely funded by state or regional subsidies, the remainder being provided by the company participating in the agreement. On occasions, when preparing the budgets for executing agreements with Industry, there is a feeling of lack of clarity on the part of the PRB, which does not clearly and reasonably establish where the development costs come from. This fact gives rise in industry to the feeling that a surcharge is being paid for the projects, directly leading to arguments over the ownership of results and this ends up with negotiations reaching a stalemate.

For its part, industry, irrespective of whether or not there are any disagreements in preparing the budgets, arguably a relatively easy problem to resolve, is inclined to wish to retain ownership of the results for itself. In this way, it obviates who is defraying most of the project, generally the public institutions, and by signing the agreement it is accessing the temporary use of know-how of a research group, for the creation of which public funding has also been necessary. The assignment of ownership to industry results, to a certain extent, in the fact that the know-how of the PRB is compromised for the future, a situation increasingly less tolerated.

In the Bayh-Dole Act -1980-, the US government, aware of the disagreements caused by ownership of industrial property rights in reaching of collaboration agreements, established that ownership would always fall to the PRB. It thus implemented what they regarded as an incentive for those public institutions that actively participated in developments co-funded by the Federal Government and industry. In this way, today even when a development is 40% funded by the Federal Government and 60% by the Company, ownership of the industrial property rights always and automatically falls to the PRB.

The imposition of this type of measures has been considered to be of value by different discussion fora in the United Kingdom[25,26], although concerned that adopting them may place at risk the collaborations currently established with Industry. In the case of Spain, the Draft of the Science and Technology Act, in its section 28, although favourable to this stance, makes it clear that ownership should always fall on the PRB *"without prejudice to the agreements by virtue whereof it has been possible to transfer or attribute rights over those results and over the industrial property applications or rights whereby they are protected".*

Furthermore, in the early phases of development of a technology it is usually appropriate to promote public-private collaboration as an effective marketing channel. In this way the results derived from this kind of collaboration are licensed to or assigned in favour of the collaborating company or companies in exchange for a fair compensation.



Promoting the industrial fabric

The Innovation Model, that must favour the involvement of PRB in company creation, is not a simple system to implement, basically due to the great complexity involved in the process of forming a company. One of the USA's most successful OTT in technology transfer, MIT (Massachusetts Institute of Technology), strongly supports the Licensing Model, aiming for a broad dissemination of knowledge and opposed to the generation of spin-offs in view of the complexity involved.

In contrast, other universities such as Oxford have strongly committed to both models, placing special emphasis on the generation of spin-off companies as a way of taking those technologies to the market, which would otherwise never have made it, and of boosting regional development. The success of this support is obvious and 95% of its spin-off companies have been capable of attracting private capital, whilst a third of UK universities have not achieved this support for the spin-off companies created under their watch. The latter situation, which is essentially a reflection of what happens both in Andalusia and in Spain, is indicative of the waste of public resources and how, in the case of the University of Oxford, commitment to quality benefits the "Innovation Model".

Support for this Model must be considered as an important tool for strengthening the industrial fabric for the following reasons:

1. Generally, the inventions devised in the PRB are very far from potential application when the concept and economic feasibility testing of the project are still to be determined. In these circumstances, it is incredibly difficult to attract industry interest in investing in the development of the technology or even in reaching licensing agreements. Furthermore, when transfers are made in these very embryonic stages the conditions imposed by industry are not very favourable to the PRB, due to the reduced value of the inventions. Hence, the creation of spin-offs enables:

   - Taking development of a technology outside of the PRB, since in this phase the approach does not always match the objectives and culture of the institution where it was initially generated.
   - Access to funding which would otherwise not be available.
   - Provision of new opportunities for enterprising scientists.
   - Creation of new jobs and the contribution of business experience for scientists joining the project from the PRB.

2. It is very frequent that the technology available in the PRB is in the form of *"know-how"*, which is difficult to transfer since it is seen by Industry as something excessively intangible. The creation of spin-off companies is thus the most appropriate form of transfer, promoting regional industrial development.

3. Spin-off companies tend to have very close links with the PRB from which they emerged, thus encouraging public-private collaboration agreements. This is one of the main reasons why spin-offs usually remain physically close to their PRB.

4. From a purely economic standpoint, spin-offs tend to provide more profits to the PRB than the licensing system and even contribute to minimizing the monopoly of large companies, thus favouring competition. Indeed, Bayh-Dole argued for legislation setting out that the transfer process should be carried out with a level playing field for both SME's and large companies[27].

Unfortunately, this model is not simple to apply and the PRB's technologies require for their development the specialized support of areas such as industrial property, marketing, finance, legal and business development, in addition to certain business skills that a priori are not necessarily found in the initial search group nor in their PRB.

On the other hand, outsourcing these capabilities is too costly and even where these are contracted out, the resulting contribution does not necessary meet the demands of the research groups, since in these initial phases companies require a higher level of specialization than isn't necessarily going to be found in a service provider.

In short, the main difficulties of the Innovation Model as regards generation of spin-off companies are:

A. Difficulties in access to funding.

B. Lack of basic skills for the correct running of the company.

Notes

27. 35 U.S.C. Chapter 18 y 37 C.F.R. Part 401.

A) Difficulties in access to funding.

Once a spin-off has been created with the main objective of carrying out the concept testing to demonstrate the feasibility of its project, from the technical and market standpoints, the difficulty in accessing funding is one of the aspects that most seriously affect them. This drawback impacts on a fundamental stage of the Innovation Model which does not end but rather starts with the formation of the new company.

In their initial stage, spin-off companies must immerse themselves in a process to validate and grow their technologies. This process is of indeterminate length depending on the sector type in which it occurs. These development periods may reach 2 years for ICT, and may reach 5 years in the case of inventions relating to biotechnology or biohealth areas. Likewise, the capital required (Seed capital) to execute the concept testing usually ranges from €100,000 to €5 million, where the higher amounts are required for those spin-offs belonging to the health sector. These sums are excessive for entrepreneurs and are generally too low for venture capital, which is usually not prepared to run the excessive risk inherent in this concept testing.

Little by little, increasing numbers of venture capital companies are appearing specializing in the biotechnology or biohealth sectors. Ysios Capital Partners is one of the first independent venture capital companies in Spain, which provides funding to young companies in the field of human health and biotechnology. However, its investments are in the range of €0.5 to €5 million. This leaves an evident shortfall to be filled with public administration's help.

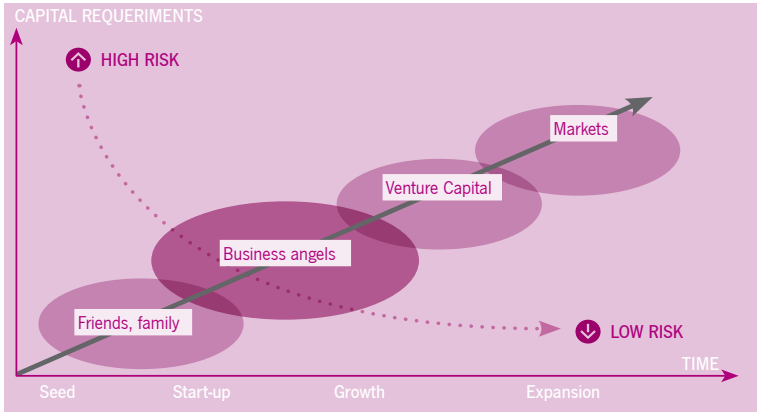
Another of the possible alternatives to make up for this lack of resources are the Business Angels networks, that have considerably extended in Europe in recent years, but having only a token presence in Andalusia until now. Malaga Business Angels is one of the few initiatives of this type that exist in our Region, which is promoted by the Planning and Development Society, SOPDE SA and co-funded by the Regional Ministry of Economy, Innovation and Science of the Andalusian Regional Government.

These networks, which in Spain are particularly evident in Madrid and Barcelona, are mainly formed by entrepreneurs and former executives that may or may not financially support young companies (€90,000-€600,000)[28] and who, in any case, give them the benefit of the knowledge that they have acquired over the course of their professional life. However, the inadequate biotechnology and biohealth business fabric that has existed and currently exists in Andalusia hinders the emergence of Business Angels with the desire to support such a complex sector. Furthermore, the very embryonic state of these networks in our region makes it complicated for them, at least for the time being, to exert a determining influence on the development of Andalusian spin-off companies.

One of the most important public initiatives aimed at creating spin-off companies is the Campus Programme from the IDEA agency (Agency for Innovation and Development of Andalusia), which has the aim of promoting the creation of Technology Based Companies within the universities. After the IDEA agency has evaluated a business project which has been put forward, and their feasibility has been determined, fledgling companies are awarded a loan of up to €100,000, with the company providing 30% of the funding. This sum, even though it may be more than sufficient for concept testing in companies from some sectors, may be insufficient for the biotechnology area. Indeed, in the United Kingdom during 2001, the spin-off support system, University Challenge Seed Fund, allocated 71% of its resources to subsidies that were mainly around £100,000 and £250,000. And although these figures are considered by the fund as excessive for performing concept testing in certain areas, it should serve to indicate that it is essential to increase public sector subsidies in this area.

Notes

28. EBAN (European Business Angels Network), 2005.



Funding Stages

Source: EBAN
(European Business Angels Network)

B) Lack of basic skills for the correct running of the spin-off companies.

Another of the fundamental aspects that is going to determine the success or failure of the spin-off lies in whether they have basic management tools for their good development and operation. In this regard, the support programmes for the creation of spin-off companies, aware of this lack, generally provide resources for business training for entrepreneurs, although professional experience, as well as a network of contacts, are not tools that can be acquired in the classroom.

In this sense, the selection process intended to determine what projects should give rise to companies, as well as at what time they should be created, are questions that require a high degree of professionalization and knowledge of the specific sectors in which the future company will operate. The specialization, professionalization and selectivity of the human teams involved in this selection process are behind the success of companies such as Isis-Innovation and SOPARTEC.

It is striking that although Spain lags very far behind in the transfer indicators (collaboration agreements, patent applications, licencing agreements, return on research) in relation to other neighbouring countries, such as France and the United Kingdom[29], this backwardness is much less evident in the creation of spin-off companies. Specifically, in 2006, 142 spin-offs were created in Spain, whilst 187[30] were created in the United Kingdom. This fact should, on the one hand, encourage us, since it evidences the existence of an increasing spirit of enterprise in Spain, but at the same time some reasonable doubts remain as to how well things are being done with regard to the promotion and creation of spin offs. We should not forget that commitment to the Innovation Model must focus on quality and not quantity.

Notes

29. Red OTRI Annual Report 2008.
30. Sainsbury Review 2007.

SUMMARY OF THE CURRENT SITUATION IN ANDALUSIA

In recent years, different **Andalusian research groups** have stood out for their contributions to advanced therapies, participating in **national and international initiatives**

We can highlight, for example, the outstanding role performed in the Thematic Networks of Cooperative Research in Health (RETICS) promoted by the Carlos III Health Institute or the Networking Biomedical Research Centre (CIBER), where researchers from our region have been leading precisely those initiatives related to cell therapy or genetics and rare diseases and we also draw attention to the recent development in Andalusia of our own embryonic cell lines or the remarkable number of clinical trials with stem cells that are being carried out in centres in our region.

A significant number of **therapeutic or diagnostic** options, related to the achievements here In Andalusia, have been incorporated into the Public Health System. This represents pioneering progress in the National Health System, as in the case of preimplantation genetic diagnosis or, within this technique, the selection of an identical sibling HLA for therapeutic purposes, as well as the outstanding impetus concerning the storage of umbilical cord cells for allogenic use, which has made the Malaga Bank the first Spanish bank and the fifth in the world in terms of sample numbers.

These contributions to scientific progress and healthcare activity have occurred in a context where **Andalusian society** has repeatedly demonstrated a very favourable sensitivity to this and where different institutions have expressed their increasing commitment to the promotion of these therapies. This situation has brought about different specific actions.

Thus, the effort made in Andalusia in recent years to promote research, development and innovation in the biomedical field can be classified as extraordinary and it has singularly, although not exclusively, concentrated on developing research programmes in the areas corresponding to the following advanced therapies: cell therapy and regenerative medicine, clinical analysis and genomic medicine and nanomedicine.

The clear political will to encourage these areas of knowledge, development and innovation has been particularly reflected in legislation development and budgetary effort, making it possible to come a significant way in these areas, although they are at different points in their development.

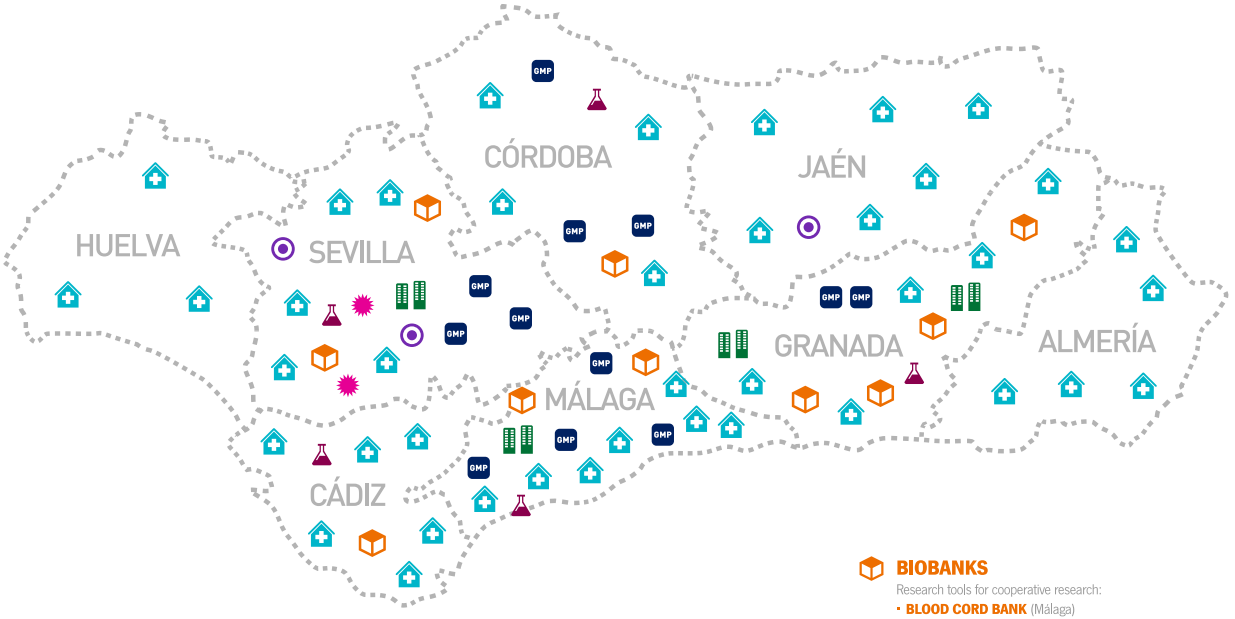
In the **legislative field**, approval of the following legal provisions can be highlighted:

- Act 7/2003, of 20 October, regulating research in Andalusia with human pre-embryos, not viable for in-vitro fertilization.
- Decree 364/2003, of 22 December, regulating the organization, composition and functioning of the Research Committee with Human Pre-embryos and the authorization procedure of projects and research centres with surplus pre-embryos from in vitro fertilization.
- Decree 156/2005, of 28 June, regulating Preimplantation Genetic Diagnosis in the Andalusian Public Health System and creating the Andalusian Committee for Genetics and Reproduction.
- Act 1/2007, of 16 March, regulating research in cell reprogramming for exclusively therapeutic purposes.
- Act 11/2007, of 26 November, Regulating the Genetics Council, in protection of human DNA banks in Andalusia and the rights of people undergoing genetic analysis.

The budgetary effort has been reflected in various specific calls to finance research projects in these areas, the implementation of training programmes in these fields, the recruitment of research groups, the creation of a network of clean rooms for preparing medicinal products in advanced therapies under good manufacturing practice standards and the start of several clinical trials, among other actions.

But, above all, this effort has been translated into agreements reached between the Regional Ministry of Health and the Regional Ministry of Economy, Innovation and Science with different Andalusian universities and, in some cases with the CSIC (Spanish National Research Council), the ISCIII (Carlos III Health Institute) or companies from the pharmaceutical sector to build benchmark monographic research centres for the Programmes of *Cell Therapy and Regenerative Medicine* (CABIMER: Andalusian Centre for Molecular Biology and Regenerative Medicine in Seville), *Clinical Genetics and Genomic Medicine* (GENYO: Pfizer-University of Granada-Junta de Andalucía Centre for Genomics and Oncological Research in Granada) and *Nanomedicine* (BIONAND: Andalusian Centre for Nanomedicine and Biotechnology in Málaga), or to build the Andalusian Centre of Excellence for Research into Innovative Medicines (MEDINA in Granada) and for the promotion of this type of research in the health research institutes linked to Andalusian University hospitals, such as the IBIS in Seville and IMIBIC in Cordoba, or in other Andalusian hospitals. Research support centres have also been created, such as Tumour, DNA, umbilical cord blood biobanks and the Andalusian Bank of Stem Cell, the Central Node of the National Cell Line Bank (BCNL), as well as a network of public GMP laboratories for the manufacturing of advanced therapy medicinal products. Furthermore, the Regional Ministry of Health, in collaboration with the Ministry of Health and Social Policy, is running in Granada a training programme in advanced therapies which is pioneering in Europe. And recently, it announced the creation of the Andalusian Cell Reprogramming Laboratory and the implementation of the Medical Genome Project, with the creation of a high-performance sequencing platform in order to prepare a reference standard of the human genome and identify genes responsible for genetically based diseases.

Map of biomedical research and healthcare resources in Andalusia



HEALTH RESEARCH INSTITUTES

Research centres linked to university hospitals to promote translational research:

- **IMIBIC** Maimonides Institute for Biomedical Research (Córdoba)
- **IBIS** Biomedical Research Institute (Sevilla)
- **CÁDIZ** Biomedical Research Institute
- **MÁLAGA** Biomedical Research Institute
- **GRANADA** Biomedical Research Institute

SPECIALIZED RESEARCH CENTRES

- **CABIMER** Andalusian Centre for Molecular Biology and Regenerative Medicine (Sevilla)
- **GENYO** Pfizer-Universidad de Granada-Junta de Andalucía Centre for Genomics and Oncological Research (Granada)
- **BIONAND** Andalusian Centre for Nanomedicine and Biotechnology (Málaga)
- **MEDINA** Research Centre in Innovative Medicines (Granada)

NETWORK RESEARCH CENTRES

Structures to promote the investigation:

- **CEAS** Excellence Centre in Research about Olive Oil and Health (Jaén)
- **CAIT** Andalusian Research Centre in Nicotine Poisoning (Sevilla)
- Andalusian Research Center in Physical Activity, Health and Sport (Sevilla)

BIOBANKS

Research tools for cooperative research:

- **BLOOD CORD BANK** (Málaga)
- **DNA BANK** (network centre, Granada is the central node)
- **STEM CELL BANK** (Granada)
- **TISSUES** (Málaga, Cádiz, Sevilla, Córdoba y Granada)
- **TUMOURS BANK** (network centre, Granada is the central node)
- **BIOLOGICAL FLUIDS OF HUMAN NEUROGICAL DISEASES** (Sevilla)

HEALTHCARE CENTRES

Providing healthcare and developing research:

- **41** Hospitals
- **1,514** Primary Care Centres

GMP FACILITIES

Fitted in compliance with European Good Manufacturing Practice:
4 (Málaga) · **3** (Sevilla) · **3** (Córdoba) · **2** (Granada)

SPECIALIZED LABORATORIES

MGP Medical Genome Project (Sevilla)
LARCEL Andalusian Cellular Reprogramming Laboratory (Sevilla)

The agreements of the Regional Ministry of Health with the Ministry of Health and Social Policy are particularly relevant for promoting research in regenerative medicine, reflecting the leadership of our region in this field and ensuring the availability of considerable resources in recent years for this research.

The Regional Ministry of Economy, Innovation and Science has also deployed a powerful set of tools, both financial and support, which are contributing to the current development of some of these projects and, above all, they can offer excellent support for future initiatives. The calls for subsidies for projects of excellence, the Plan Insignia, the Technological Corporation of Andalusia or programmes such as Talentia, help to define a scenario of unprecedented opportunities in our Region

Likewise, the Regional Ministry of Health through Fundación Progreso y Salud and the group of local foundations for health research in the Andalusian Public Health System (see annex 2), is facilitating numerous instrumental mechanisms to facilitate the research work such as the International Project Office, the Office of Technology Transfer or the training and return programmes of researchers such as those established with the US National Institutes of Health or Michigan State University, the latter exclusively oriented towards cell reprogramming.

Highly significant is the increasing presence in these projects of the business sector, both pharmaceutical and biotechnology, as is the case with Pfizer, MSD or Genetrix, among others. It is also important to attract sector companies to Andalusia to invest in their own R&D projects in areas convergent with those tackled by the Andalusian Initiative for Advanced Therapies. CELGENE is one such company to announce recently the creation of the Celgene Institute for Translational Research Europe-CITRE in Seville. The contribution and the role of industry is crucial for closing the R&D circle, not only generating knowledge and benefits for health, but also facilitating considerable social and economic development for Andalusia.

Finally, we should emphasize the encouragement that Andalusian society has been giving to this initiative. An example of the support given to some of the projects is the charitable support of financial institutions or their foundations , as is the case of savings banks in our region such as EL MONTE (now CajaSol) or LA GENERAL (now Caja Granada).

Summary of results in scientific production and knowledge transfer in Andalusia

As a result of this multisector effort over recent years, the Autonomous Region of Andalusia today is positioned nationally as one of the most active in Advanced Therapies, highlighting the attraction of competition funds for implementing the creation of infrastructures and training programmes, as well as for the performance of cutting-edge clinical trials, among other activities.

In terms of its human capital, the Andalusian Initiative for Advanced Therapies, in collaboration with the Fundación Progreso y Salud, has identified and contacted 239 researchers (see annex 3) with scientific involvement in areas related to Advanced Therapies, both in their more basic research stage or in their clinical stage. These researchers have been identified through the databases that include the Principal Investigators of the projects presented in calls for subsidies put out by the Regional Ministry of Health in the field of advanced therapies. This list only makes up part of the group of researchers carrying out lines of research related to this field in Andalusia, and also incorporates people who are currently not active in research, but this was the only source of information available. This limited information makes

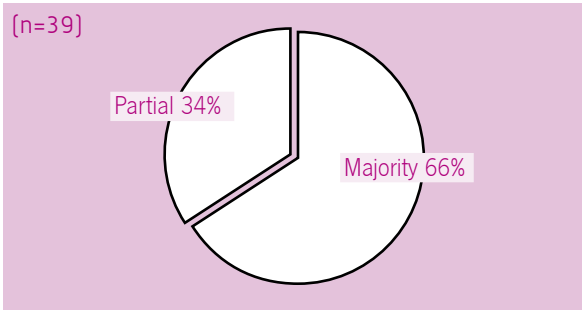
it clear that the first line of action proposed by this plan must be to create a research group register (action 1.1). To contextualize this information, according to the latest estimations, the total population of research groups in Andalusia[31] stands at 1,769, with an approximate average size of 10 researchers per group.

Some of the data presented below has been prepared from a sample of 16.3% of the researchers identified, formed by those who answered the questionnaire[32]. This unrepresentative sample may, however, serve to give a general idea or approximation of the scientific activity being performed in this field in Andalusia.

Within the three areas of research in advanced therapies existing in Andalusia, over half of the cases of researchers contacted were active in the area of Clinical Genetics and Genomic Medicine, something less than 5% were active in the Nanomedicine area and the remaining cases worked in Cell Therapy and Regenerative Medicine.

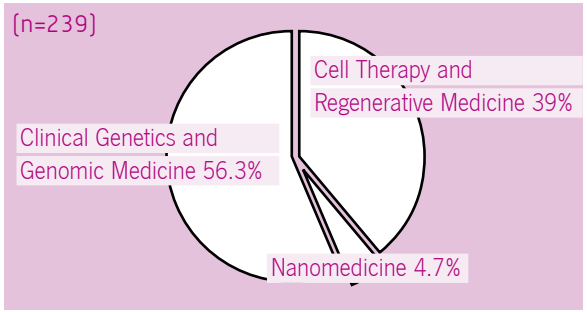
The researchers were asked about their degree of dedication within the areas of Advanced Therapies. Two thirds of the total reflected majority dedication to this field.

Degree of dedication in advanced therapies

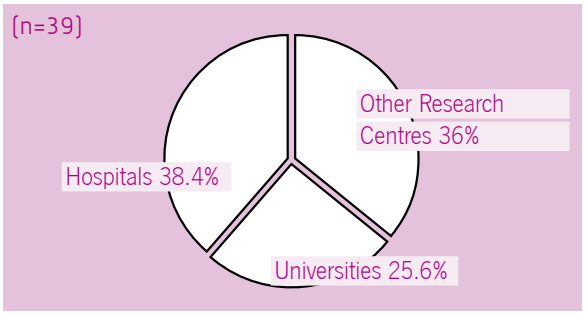


With regard to the placement of researchers, most work in hospitals in the Andalusian public health system and Universities.

Ratio of researchers by areas



Type of body researchers are assigned to



Notes

31. Ramos-Vielba I, Fernández-Esquinas M, Espinosa-de-los-Monteros E. 2009. Measuring university-industry collaboration in a regional innovation system. Scientometrics. DOI 10.1007/s11192-009-0113-z.

32. A questionnaire was supplied including 15 questions related to different aspects of work in advanced therapies, scientific production and participation in working networks, as well as involvement in technology transfer and clinical practice. The questionnaire was sent to 239 researchers due to their leadership in projects related to the different areas of advanced therapies and/or their assignment to related research centres. The questionnaire was sent on two occasions and the number of researchers that answered was 39, representing a sample of 16.3%.

Aside from Hospitals and Universities, the researchers worked in diverse placements, including Biomedical Foundations, Biobanks and other research centres.

Within the various research lines in Andalusia, research at all stages was being carried out, from more basic science to participation in clinical trials. Almost one third of researchers said they had participated in some type of clinical trial. Annexe 4 details projects related to Advanced Therapies awarded by the Regional Ministry of Health of the Andalusian Government with an average funding per project of €74,822. This list does not include the research projects funded by the Regional Ministry of Economy, Innovation and Science, or other private or public institutions.

The following table gives a partial list of the various lines of work being carried out in the area of Advanced Therapies defined by the researchers themselves, highlighting the number devoted to cancer, neurosciences and metabolism.

Research lines performed in Andalusia by subject area

NEUROSCIENCES
Genetics of neurological and psychiatric diseases.
Cell therapy in neuropathologies (ataxias and epilepsy).
Chromaffin cell lines with neurotrophic action as therapy for Parkinson's disease.
Epigenetics and pharmacogenetics in neurodevelopment diseases, in particular ADHD and early onset of schizophrenia. Relation of gene expression with neuroimagine.
Molecular mechanisms that cause autism and general development disorders.
Physiopathology, genetics and new experimental therapeutic targets in mental disease, clinical trial in patients with Fragile X syndrome.
Neuropsychopharmacology of lipid transmitters for the study of neural genesis and conduct.
Pharmacogenomics and proteomics of the response to IFN-beta in patients with Multiple Sclerosis.

METABOLISM
Molecular basis of insulin resistance, obesity and type 2 diabetes, role of adipose tissue.
Obtaining insulin-producing cells from stem cells for their use in cell therapy of Diabetes Mellitus.
Functional role of orphan nuclear receptors in regenerative and degenerative processes.
Cell therapy of Diabetes Mellitus. Epigenetics, cellular and molecular biology.
Cell therapy in hepatic regeneration and inflammatory disease.
Cell therapy in experimental glomerulopathies.
Functional study of the orphan nuclear receptors involved in obesity and diabetes.
Regeneration of beta-pancreatic cells as therapy for Diabetes Mellitus.
Cell therapy of Diabetes Mellitus.

Research lines performed in Andalusia by subject area

(Cont.)

CANCER

New drugs in the treatment of cancer, translational studies.

Role of extracellular proteolysis in cancer processes.

Mechanisms of progression and metastasis of cancer by circulating tumour cells.

Stem cells, cancer and development.

The escape of cancer to immune response.

Gene therapy of cancer to increase immunogenicity in tumour cells.

Functional genetics of cancer.

OTHER

Cell therapy in the field of transplant of haematopoietic precursor cells. Mechanisms of genetic susceptibility to the development of fungal infections.

Impact and control of the mobility of mobile DNA elements in the human genome.

Search for molecular mechanisms responsible for different biomedical problems (cancer and rare metabolic and inflammatory diseases) by biocomputational and experimental approaches (including functional genomics and proteomics). New diagnostic, prognostic and treatment strategies.

Human embryonic stem cells and iPS, differentiation and cell reprogramming.

Genetic resistance to infectious disease (AIDS and hepatitis C).

Control of the differentiation of embryonic stem cells.

Cardiovascular development and angiogenesis.

Development, regeneration and repair of the cardiovascular system.

Applied pharmacogenomics.

Regulation of embryonic cell differentiation.

Skeletal tissue engineering based on cells, biomolecules and nanomaterials.

Design and synthesis of nanoparticles with biomedical applications.

Of the possible ways of assessing **research activity**, the following indicators were chosen:

- Number of publications, only including those journal publications that comply with a minimum set of quality demands according to the Institute for Scientific Information and registered in the Science Citation Index or in the Social Citation Index. The inclusion criteria include the international character of the journal and the associated citation data, among other parameters.

- Index h[33,34] indicator derived from the number of citations from the different publications throughout a researcher's career. The method defines index h as the number applied to a researcher who has h pieces of work and has been cited at least h times. For example, h=10 means there are ten articles which have 10 or more citations, but there are not 11 with 11 or more quotes.

- Publication in journals of the first quartile of impact within the specialization.

The scientific productivity values of researchers working in any of the areas related to Advanced Therapies was outstanding for all indicators, both in those that indicated their majority dedication and those that indicated partial dedication, in many cases as a consequence of healthcare practice in the Andalusian Public Health System. Ten percent of the Principal Investigators consulted had over 100 publications in international journals.

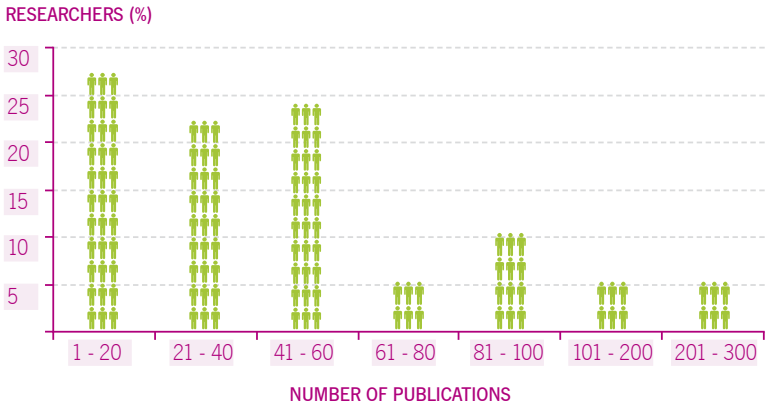
Notes

33. Hirsch, J. E. (2005). "An index to quantify an individual's scientific research output". PNAS 102 (46): 16569–16572.

34. Imperial J, Rodríguez-Navarro A. 2007. Usefulness of Hirsch's h Index to Evaluate Scientific Research in Spain. Scientometrics 71: 271-282.

Scientific production levels according to number of publications

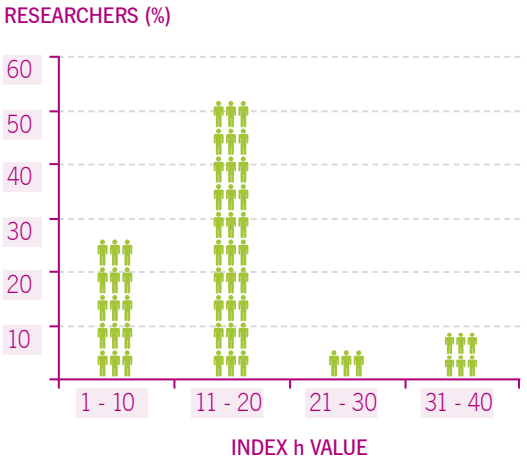
n=36



The degree of importance of the publications, measured as index h of the group of researchers consulted was of even greater impact, given that 18% had an index h greater than 25.

Scientific production levels according to index h

n=28



This fact was corroborated by the impact index of the journals in which many of the scientific works were published, within the first quartile of the different specializations.

Much of the research carried out in Andalusia in Advanced Therapies requires a multidisciplinary approach or has the challenge of an approach of greater geographic scope. For this reason there are numerous scientific working networks involved. The following table shows some networks with the participation of researchers located in Andalusia performing research lines in Advanced Therapies.

RESEARCH NETWORKS

RETICS:
Cell therapy network

RETICS:
Multiple Sclerosis research network

RETICS:
AIDS research network

RETICS:
Cardiovascular diseases research network

RETICS:
Hearing Disorders research network

RETICS:
Renal research network

RETICS:
Spanish Mastocytosis Network

CIBER:
Bioengineering, Biomaterials and Nanomedicine

CIBER:
Hepatology

CIBER:
Diabetes and Associated Metabolic Diseases

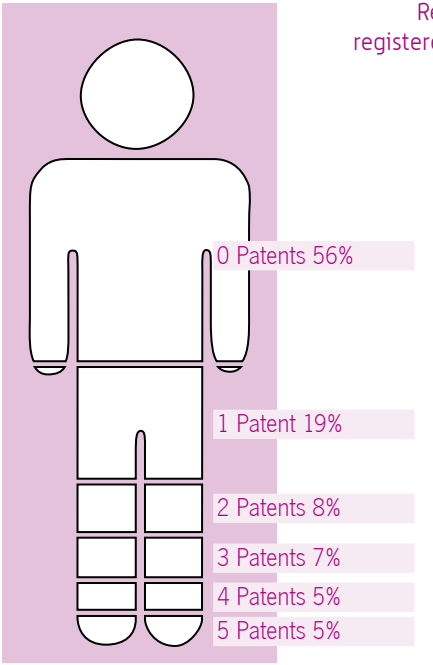
CIBER:
Mental Health

CIBER:
Physiopathology of Obesity and Nutrition

With respect to knowledge transfer, somewhat less than half of the researchers consulted indicated that they had generated any patents whilst almost one third indicated that they had been involved in business projects, either leading them, with specific collaborations or by contracts mediated by transfer offices. Although most business projects executed were as start-up and SMEs, there were also cases of collaboration with large pharmaceutical companies.

Researches with registered patents (%)

n=39



The percentage of researchers who indicated interactions with companies was 30.7%, a figure that contrasts with a recent survey published in Nature Biotechnology[35,36] where over half of the 3000 researchers surveyed in the USA stated some type of company relation, ranging from consultancy reports to marketing contracts up to the creation of companies.

Notes

35. Darren E. Zinner, Dragana Bolcic-Jankovic, Brian Clarridge, David Blumenthal and Eric G. Campbell. 2009. Participation Of Academic Scientists In Relationships With Industry. Health Affairs. 28: 1814-1825.

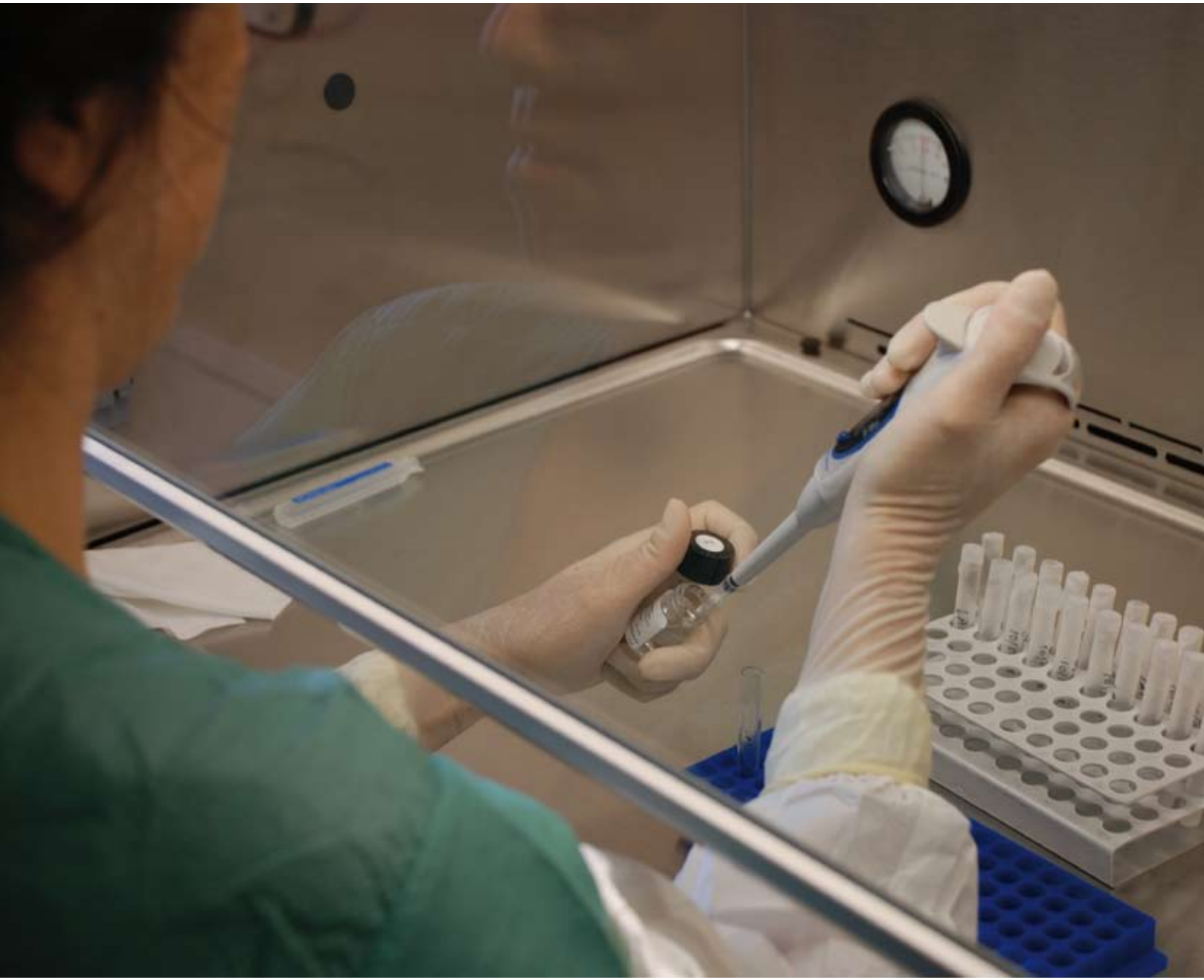
36. Shaffer C. 2009. Report concludes industry-academia partnerships on the wane. Nature Biotechnology. 28: 7-8.

The following table details some of the companies created and/or companies with which contracts or other types of interaction have been established.

Companies created or with which collaborations or contracts have been established
CYTOGNOS S.L.
LOBITEC INTERNACIONAL S.C.
LABORATORIOS ESTEVE S.A.
CARDION AG
LORGEN GP S.L.
BLASTICON BIOTECHNOLOGISHE FORSCHUNG GMBH
VIRCELL S.L.
NEOCODEX S.L.
PHARMAMAR S.A.
INSTITUTO BIOMAR S.A.
OIKOS INTERNACIONAL LTD
MOLOGEN AG
BIOCLINIC S.L
BIOBEVAN S.L.
MERCK, SHARP & DOHME DE ESPAÑA S.A.

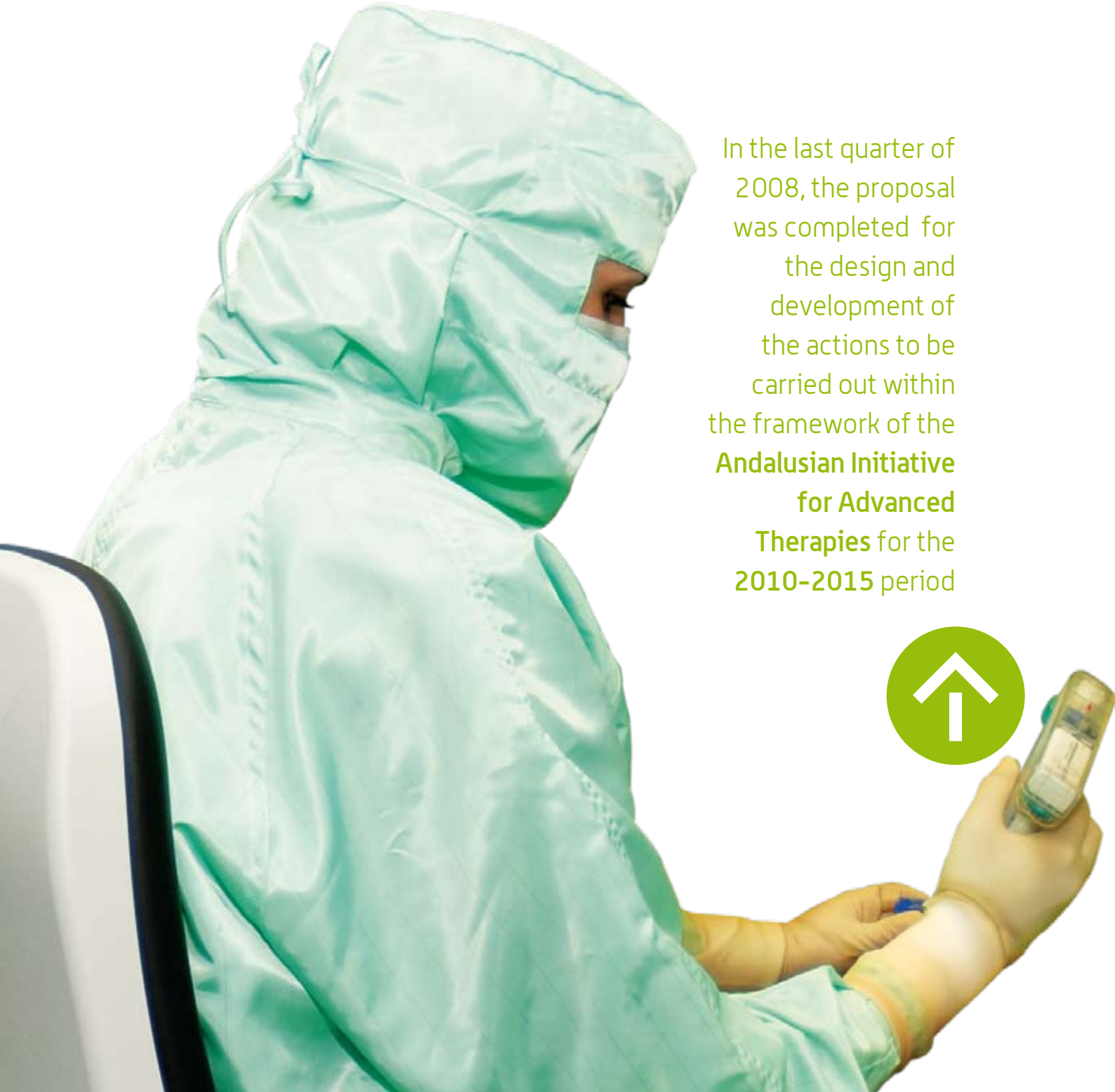
Finally, annexe 5 shows the biotechnology companies from the biomedicine sector in Andalusia, according to data from the Regional Ministry of Economy, Innovation and Science provided in December 2009.

On the basis of analysis of the situation in our region, it can be concluded that Andalusia has already taken decisive steps to promote R&D&i in the area of advanced therapies and is ideally placed, with suitable resource orientation and planning to try to achieve for itself, as we have already argued in the initial justification, a commanding position in the field of biomedical research and for this research to become one of the revitalizing elements of quality and healthcare innovation, whilst at the same time promoting our business framework and our economy.



4

WORKING METHODOLOGY



In the last quarter of 2008, the proposal was completed for the design and development of the actions to be carried out within the framework of the **Andalusian Initiative for Advanced Therapies** for the **2010-2015** period

This methodology included different phases of preparation throughout 2009, defining the areas to be covered as well as the bodies that will develop it.

The first step consisted of approval of the methodology by the Governing Committee who defined the mission, vision, strategic principles and objectives on 25 February 2009, the date on which the Advisory Committee, too, was established. It also designated the coordinators of each of the participating Working Groups.

Below, we show the areas in which it was decided to structure the planning work of the Andalusian Initiative for Advanced Therapies, the bodies taking part in their preparation, the coordinators designated for the Working Groups that have participated in the preparation, the fundamental aspects that each working group has tackled, the phases for the preparation of the strategy and action plan and the responsibilities that lie with each participating body.

A) Areas tackled by the Andalusian Initiative for Advanced Therapies

The initiative is structured around 5 areas:

1. Knowledge generation – research
2. Knowledge dissemination – training
3. Knowledge application – development of medicinal products/clinical trials
4. Knowledge transfer – access of new therapies to the market
5. Strategic forecast, funding and evaluation of the Initiative

B) Bodies that define the Strategy and Action Plan of the Andalusian Initiative for Advanced Therapies

Governing committee. Composed of:

- The Secretary General of Quality and Modernization of the Regional Ministry of Health
- The Secretary General of Universities, Research and Technology of the Regional Ministry of Economy, Innovation and Science
- The Director-General for Knowledge Management, Quality and Research of the Regional Ministry of Health
- The Director-General for Research, Technology and Enterprise of the Regional Ministry of Economy, Innovation and Science
- The Director-General for Healthcare of the Andalusian Health Service
- The Director of the Andalusian Innovation and Development Agency
- The General Manager of Fundación Progreso y Salud
- The Executive Director of the Andalusian Initiative for Advanced Therapies
- Two rotating Vice-Chancellors for research across the Andalusian Universities
- A representative of the Spanish Association of Bioenterprises (Asociación Española de Bioempresas) (ASEBIO)
- A representative from the pharmaceutical industry

Advisory committee. Composed of:

- The Executive Director of the Andalusian Initiative for Advanced Therapies
- The Directors of the research centres: CABIMER, GENyO, BIONAND and the Directors of the Research Institutes.
- The Directors of the Cell Therapy and Regenerative Medicine, Clinical Genetics and Genomic Medicine and Nanomedicine programmes
- The President of the Regional Clinical Trials Committee
- The Regional Transplant Coordinator
- Deputy Director-General for Quality and Research of the Regional Ministry of Health
- A representative from the IDEA Agency
- A representative from Fundación Progreso y Salud
- Representatives of Patient Associations
- Outstanding researchers in this area

Servicio Andaluz de Salud. Consejería de Salud. Junta de Andalucía.

Working groups:

The Governing Committee appointed a coordinator for each of the 7 working groups subsequently constituted. Each group coordinator was responsible for identifying the people forming each working group, after consulting the Advisory Committee.

Working groups 1, 2 and 3. Knowledge generation:

1. Cell Therapy and Regenerative Medicine.
   Coordinator: Dr Itziar Ochotorena

2. Clinical Genetics and Genomic Medicine
   Coordinator: Dr Guillermo Antiñolo delegating to Mr. Carlos Chinchilla

3. Nanomedicine
   Coordinator: Dr David Pozo

These groups have focused their work on preparing proposals aimed, among other aspects, at:

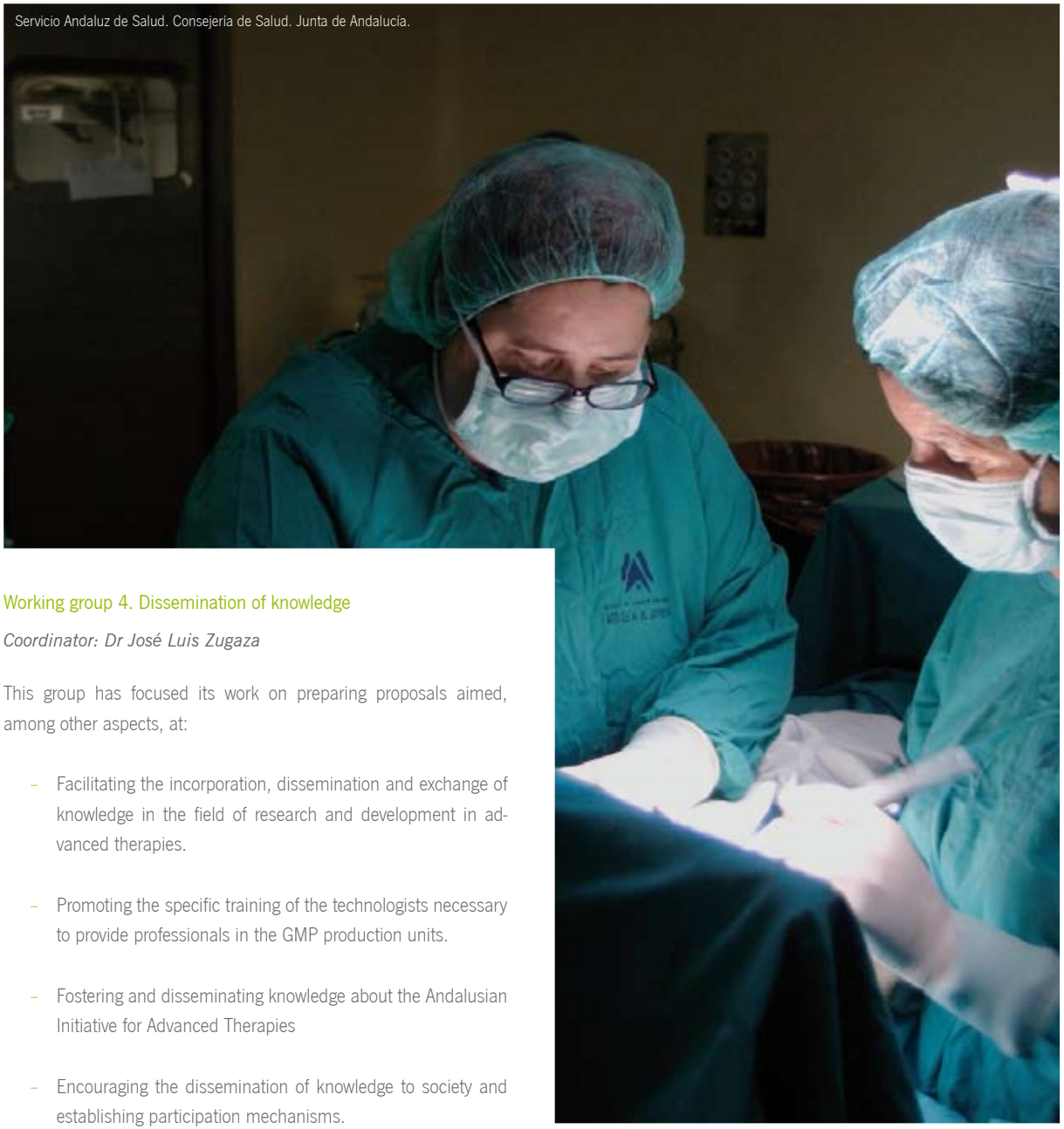
- Increasing the critical mass of basic researchers in the field of Advanced Therapies.

- Adapting infrastructures to basic research requirements and improving efficiency of their use.

- Promoting excellence in biomedical research in areas of maximum interest, together with highly creative unconventional research.

- Favouring the interdisciplinary nature and synergies between the three areas of research in advanced therapies.

- Promoting translational research in Advanced Therapies.


Servicio Andaluz de Salud. Consejería de Salud. Junta de Andalucía.

Working group 4. Dissemination of knowledge

Coordinator: Dr José Luis Zugaza

This group has focused its work on preparing proposals aimed, among other aspects, at:

- Facilitating the incorporation, dissemination and exchange of knowledge in the field of research and development in advanced therapies.
- Promoting the specific training of the technologists necessary to provide professionals in the GMP production units.
- Fostering and disseminating knowledge about the Andalusian Initiative for Advanced Therapies
- Encouraging the dissemination of knowledge to society and establishing participation mechanisms.

Working group 5. Knowledge application

Coordinator: Dr Inmaculada Herrera

This group has focused its work on preparing proposals aimed, among other aspects, at:

- Promoting the interrelation between basic and clinical researchers to enable development of translational research, the cooperation and the exchange of knowledge between groups and the carrying out of single centre or multicentric clinical trials, creating collaboration spaces and establishing a model to facilitate cooperation.
- Fostering clinical trials of quality in areas of maximum interest.
- Giving support to the carrying out of clinical trials in advanced therapies.
- Adapting infrastructures to the manufacturing requirements of research products for their clinical application and improving the efficiency of the use of such infrastructures.
- Providing the necessary support to comply with the regulatory framework, quality control organization, suitable characterization and development of products and improvement in production systems.

Working group 6. Knowledge transfer

Coordinator: Mr. Gustavo Fúster

This group has focused its work on the preparation of proposals aimed, among other aspects, at:

- Promoting mechanisms to protect and transfer results that guarantee future clinical application.
- Facilitating the marketing of the results obtained by research in advanced therapies to make them accessible to patients, who are candidates for those treatments.
- Fostering the development of its own transfer model that leads to value creation, promoting public-private association models from the earliest stages of clinical research and developing market niches in services that are ancillary to research.

Working group 7. Strategic forecast, funding and evaluation of the Andalusian Initiative for Advanced Therapies

Coordinator: Mr. Gerónimo Sánchez

This group has focused its work on the preparation of proposals aimed, among other aspects, at:

- Defining strategic forecast mechanisms that make it possible to know what international progress is being made in this research field and detect the generation of related emerging areas of knowledge.
- Designing models for the gathering of resources which will assist research groups in the development of their projects.
- Promoting a methodology for the preparation of "business plans" adapted to the mission of the Andalusian Initiative for Advanced Therapies to provide a tool for decision-making in prioritizing actions to be performed.
- Establishing Initiative's assessment methodology by establishing indicators that make it possible to redeploy resources and their strategies and objectives.

C) Phases and methodology for the preparation of the Strategy and Action Plan of the Andalusian Initiative for Advanced Therapies

4th quarter 2008: methodology definition.

February 2009: establishment of the Governing and Advisory Committees, approval of the methodology, definition of the mission, vision, strategic principles and objectives, and appointment of the working group coordinators.

March 2009: establishment of the working groups by the coordinators with the collaboration of the Advisory Committee.

2nd and 3rd quarter 2009: development of each area corresponding to each of the working groups, which should include:

- Goals set (and on what date).
- Strategies and actions to develop.
- Estimated calendarized budget necessary to perform said actions.
- Identification of the duties necessary to develop each area of the Initiative as well as the persons or organizations, both public and private, to carry them out. Where no person was in post to carry out those functions, the profile of suitable staff to be appointed to execute the strategic plan should be defined.

4th quarter 2009: preparation of the draft of the Strategy and Action Plan, including the coordinators of the working groups together with the Initiative's Executive Director, to integrate the 7 documents from the working groups.

1st quarter 2010: draft publication, suggestions received for review by the Advisory Committee and approval by the Governing Committee.

2nd quarter 2010: Organization of a symposium to present Initiative's Strategy and Action Plan. It will later be published and disseminated.

D) Duties of the Governing and Advisory Committees and the Working Group Coordinators

Governing committee

1. Approval of the present proposal for the design and development of Initiative's Strategy and Action Plan or its modification.
2. The defining of the Initiative's Mission and Vision, as well as its Strategic Principles and Objectives.
3. Approval of the appointment of the working group coordinators.
4. Approval or modification of Initiative's Strategy and Action Plan.

Advisory committee

1. Giving advice concerning composition of the working groups.
2. Giving advice on identification of the interest groups to be consulted regarding the content of the drafts from each work area of the Initiative
3. Giving advice on the preparation of the Initiative's Strategy and Action Plan.

Coordinators of the working groups

1. Establishing the working groups after consulting the Advisory Committee.
2. Coordinating the preparation of the corresponding part of the draft of each area of the Initiative.
3. Preparing, together with the Executive Director of the Initiative, the draft of the Strategy and Action Plan, comprising the 7 documents from the working groups, and the outline of duties to be carried out by the Initiative together with the people or entities in charge of the carrying out of these duties.
4. Coordinating the evaluation and response to the suggestions of the interest groups consulted.

5

MISSION, VISION, STRATEGIC PRINCIPLES AND OBJECTIVES

The Mission of the Andalusian Initiative for Advanced Therapies is to promote the **development of new therapies** in order to improve the population's health

Mission

The Mission of the Andalusian Initiative for Advanced Therapies is to promote the development of new therapies in order to improve the population's health and to incorporate advanced therapies in Andalusia as an element of innovation in the healthcare and progress of the region. We will do this by seeking alliances between the academic world, research institutions, health centres, patients' associations, biotechnological SMEs and the pharmaceutical industry.

The Andalusian Initiative for Advanced Therapies must therefore identify, organize and provide the necessary support for the maximum development of multidisciplinary research in the field of advanced therapies in Andalusia. It must facilitate the training of technologists, basic and clinical researchers, foster translational research in this field and promote the generation of a business structure beneficial to such research which will ultimately provide a source of wealth for the region and will enable the potential benefits of advanced therapies to be passed on to the population in as short a time frame as possible.

Vision

Andalusia aspires to play a relevant role in the field of Advanced Therapies, so that research, development and innovation in this field become the drivers for scientific progress, improvement of health and future social and economic development, singling out Andalusia's identity in the national and international arena.

STRATEGIC PRINCIPLES

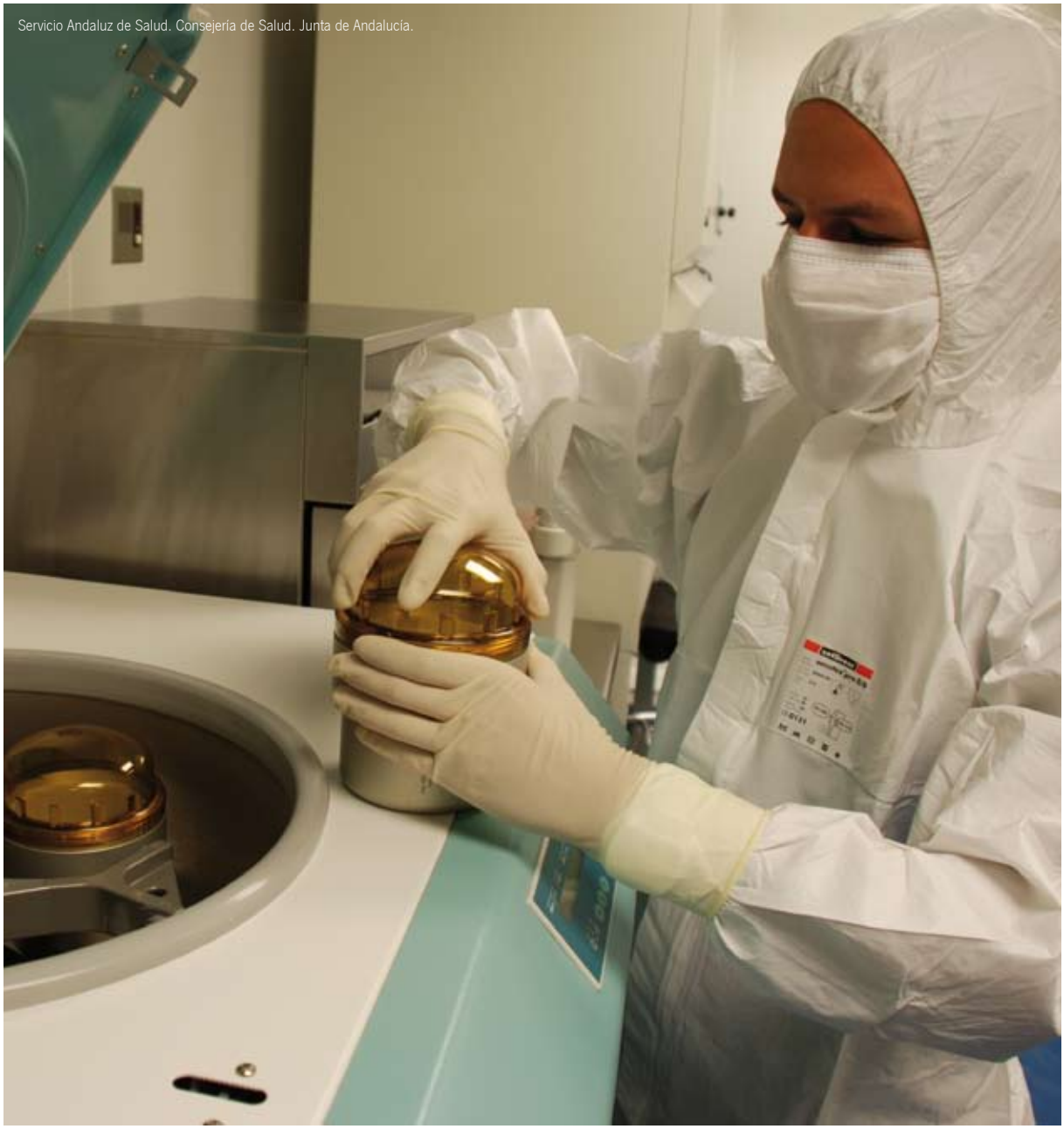
The strategic principles that inspire the Andalusian Initiative for Advanced Therapies are coherent with those of the Andalusian Plan for Research, Development and Innovation 2007-2013 (PAIDI) and the Strategic Plan for Research, Development and Innovation in Health 2006-2010, in which this Initiative is framed.

Principles of the PAIDI

1. Cooperation and Integration of knowledge in the Andalusian system (R&D&i).
2. Quality, excellence and relevance in knowledge generation.
3. Coordination and complementarity in technological development.
4. Orientated towards results.
5. Protection of knowledge generated and intellectual property.
6. Interaction and transfer between public and private areas in technological research and development.
7. Technological research and development as a comprehensive process.
8. Equal opportunities.

Strategic Lines of the R&D&i Plan in Health

1. Promoting the orientation of the research, development and innovation activities carried out in Andalusia in the biomedical area towards solving the main health problems affecting citizens in the Andalusian region.
2. Incorporating citizens in R&D&i planning in health, promoting their participation in decision making and their knowledge of and sensitization to the scientific-technical activity being carried out.
3. Reinforcing a research and innovation culture in the Andalusian Public Health System.
4. Promoting the cooperation and development of research and innovation networks between the Andalusian Public Health System and the other agents in the Science-Technology-Enterprise System with the aim of creating a Biomedical Subsystem around bioareas and bioclusters.
5. Contributing to developing structures and channels to manage the knowledge generated in the Andalusian Public Health System, aimed in the last phase to enable its transfer to the business fabric and, therefore, its transformation into social and economic progress.
6. Guaranteeing the complementary nature of the promotion actions of R&D&i activities carried out by the public health authorities with the regional, national and European programmes, under the principle of efficacy and efficiency of actions in a global context.
7. Making progress in developing an evaluation culture of scientific and technological activity.
8. Boosting the development of excellence in R&D&i around the prioritized framework lines.
9. Giving the Andalusian Public Health System the necessary human capital to develop the above strategies.
10. Guaranteeing the plan's financial sustainability.


Servicio Andaluz de Salud. Consejería de Salud. Junta de Andalucía.

Objectives

The actions this Initiative defines for the 2010 to 2015 timeframe are included in the fundamental phases of the research and innovation process i.e. generation of new knowledge and dissemination, application and transfer of the knowledge generated.

The overall objectives underpinning this Action Plan are:

1. To promote the development and application in clinical practice of new therapies fundamentally based on research results from Andalusia's three research programmes related to advanced therapies.

2. To enable fair and equal access in the population to potential new treatments.

3. To contribute to the creation of a business environment which fosters the development of advanced therapies, promoting efficient mechanisms of knowledge transfer and collaboration with the business sector.

4. To focus efforts. The ambition of the measures promoted must be to undertake a realistic analysis of the difficulties encountered in this area of research and its cost. For this reason it is necessary to concentrate our efforts on a translational approach, if we wish to create a position of real competitive advantage for ourselves in our region.

5. To foster synergies between the three research programmes related to advanced therapies: the Cell Research and Regenerative Medicine Programme, the Clinical Genetic and Genomic Medicine Programme and the Nanomedicine Programme, whose fields of knowledge show increasing overlap.

6. To facilitate alliances between all agents involved in the research and development process by encouraging open and transparent mechanisms that enable optimum use of resources and effort in this process, favouring alliances in the national and international sphere.

7. To promote the translational research approach, facilitating common instruments of support in the production and application of advanced therapy drugs, in accordance with the requirements of the regulatory bodies.

8. To facilitate the participation of scientific leaders in all areas, clinical researchers, research managers and representatives of patients' associations and the private sector.

9. To identify the needs of all agents involved in this initiative to develop tools and solutions specific to their own particular needs.

10. To contribute to the development of an evaluative culture of research and innovation, which will not only analyse results in the scientific area but also the impact of incorporating these new therapeutic approaches, and the opportunities that may arise from them, in the business sector and the Andalusian public health system.

Therefore, the Andalusian Initiative for Advanced Therapies must serve as a planning and coordination tool which, via an efficient orientation of resources and the participation of the agents involved, encourages the synergies of the three research programmes and promotes the maximum impetus for translational research. This facilitates access of the general population to new treatments in the field of advanced therapies and the development of a new high-value, productive fabric in our region.

To carry out its functions set out above, it will be decisive to have the commitment and active participation of the Andalusian Universities and other public research bodies, the Andalusian public health network, the biotechnology and pharmaceutical business sector, patient and user associations and, finally Andalusian society as a whole, whose sensitization is a key element in the future.

6

ECONOMIC MODEL

Andalusia aspires to play a relevant role in the field of **advanced Therapies**

The vision defined by the Governing Committee of the Andalusian Initiative for Advanced Therapies is for "Andalusia to aspire to play a relevant role in the field of Advanced Therapies, so that research, development and innovation in this field become the drivers for scientific progress, improvement of health and future social and economic development, singling out Andalusia's identity in the national and international arena". In order to achieve this vision, we must reinforce the value creation chain from knowledge generation to its transfer, encouraging the generation of industrial property assets, fostering public-private collaboration agreements and promoting an industrial fabric into which the technologies or know-how can be transferred.

We are, therefore, putting forward for consideration an economic model to support the proposal of results transfer and management presented in this Action Plan. This model comprises a series of initial considerations based on the following premises:

1. Andalusia as a whole has been taken as evaluation unit.
2. Sustained investment will be necessary to obtain good results.
3. Current investment levels will not be sustainable indefinitely.

To start with, the model on which the Initiative action framework proposal is based, is explained as a series of phases that will represent the evolution of the model from its initial situation to the intended final situation, incorporating new elements in the successive phases to justify the model's suitability. The chapter corresponding to the Action Plan will then explain the prioritised actions to be carried out by the Initiative to implement this model.

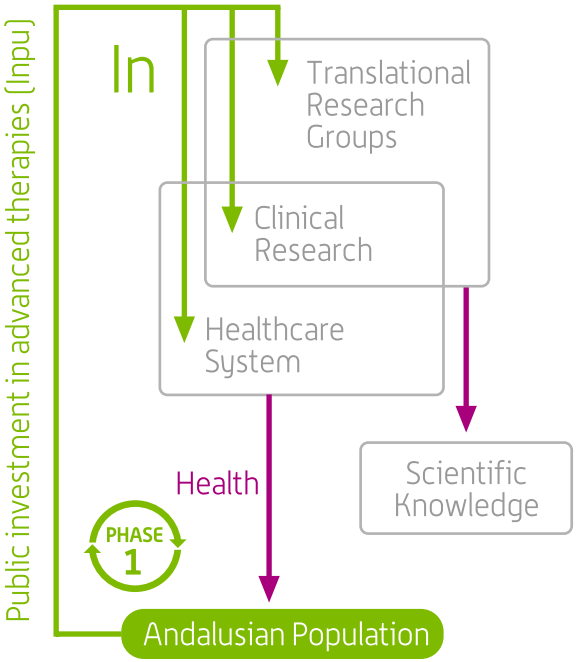
1. Explanation of the economic model

The Andalusian Government has taken on a high degree of political and financial commitment to the development of advanced therapies in Andalusia. The funds allocated to the Initiative are sourced entirely from the public purse and allocated to the two fundamental participating agents: the **research groups** and the **health system**. At their intersection we have a fundamental pillar in the process, clinical research.

These funds which, although in principle could be considered an expense, must be understood as an investment if we consider:

- The set of results generated from this initiative will, without debt, be reinvested into the Andalusian population as a whole in terms of health and scientific knowledge (Phase 1).

Ecomic Model: Evolution



PHASE 1.
LAUNCHING OF THE INITIATIVE

The Investment in advanced therapies (In) is equal to the Public Investment in Advanced Therapies (Inpu.)

The expenditure of the System in Advanced Therapies is public and is equal to the expenditure of the Research Groups + Clinical Research + Related Healthcare System

Public expenditure (Gpu.) is equal to the Investment in Advanced Therapies

In = Inpu = Gpu

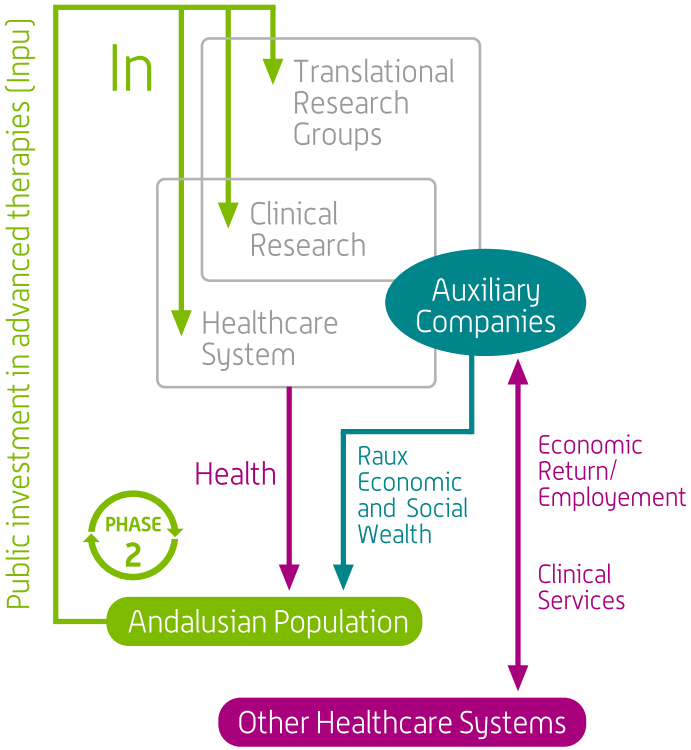
The Investment is justified by the improvement in health of the Andalusian population. It is known how much is invested, but how can we measure the health benefits?

In = Inpu = Gpu

Result (Inpu)=Health

– As a consequence of the investment made via the Initiative, it would, in the first place be possible to generate the creation of auxiliary companies to supply suitable goods and services to support the activity of the agents involved. These companies could increase their field of action to other markets outside of Andalusia. In this way they would increase the economic and social wealth of the region (Phase 2).

Ecomic Model: Evolution



PHASE 2.
AUXILIARY COMPANIES

The Investment in Advanced Therapies enables the emergence and development of related services companies.

These Andalusian companies must start competing in other markets, selling the services already offered in Andalusia to other regions. The return on these services will be to create specialized employment and economic wealth (Raux) in the region.

In=Inpu=Gpu

Result=Health+Raux

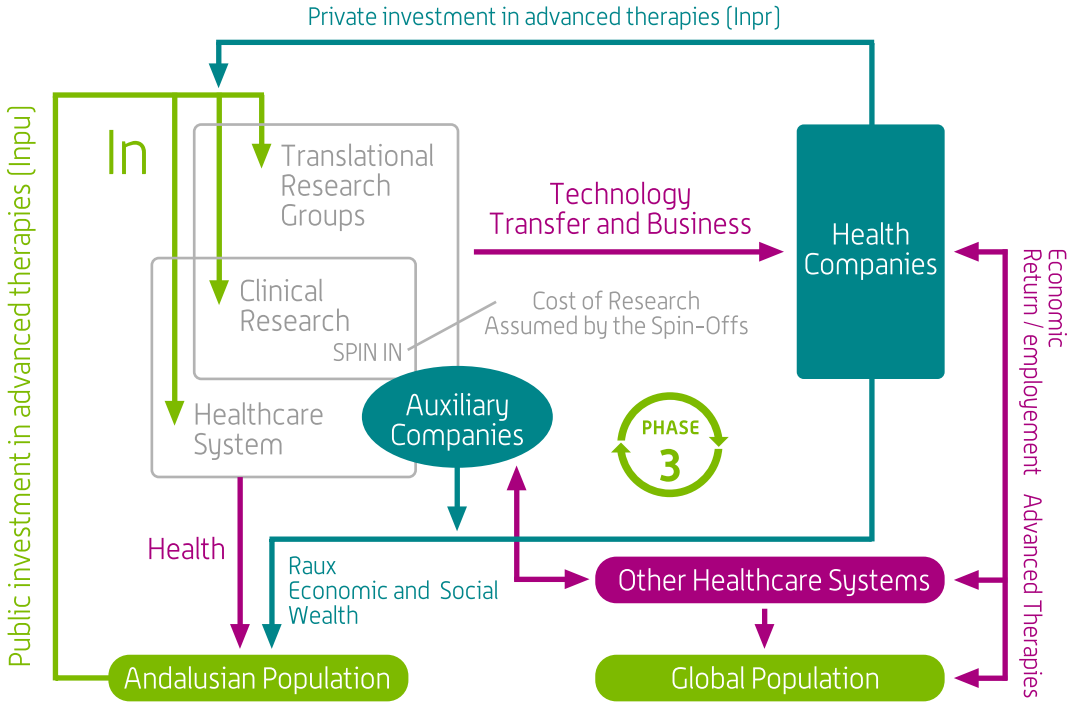
Public investment starts obtaining private results. Auxiliary Company Development Plan.

In this case, the result in the Andalusian population would be felt, not only in terms of health, but also in terms of economic and social wealth (which is in itself a primary indicator justifying the initial investment).

For this process, it is necessary to consider a development plan for these auxiliary companies to support them in their growth.

- At a later stage, the results obtained may enable the emergence and development of companies that will gather knowledge at different phases and transfer this knowledge to other regions. These companies will acquire knowledge from the public system, in exchange for the re-injection of private investment into the system. Furthermore, these health companies would benefit from economic returns and create employment, reinvesting once again in the Andalusian population (Phase 3).

Ecomic Model: Evolution



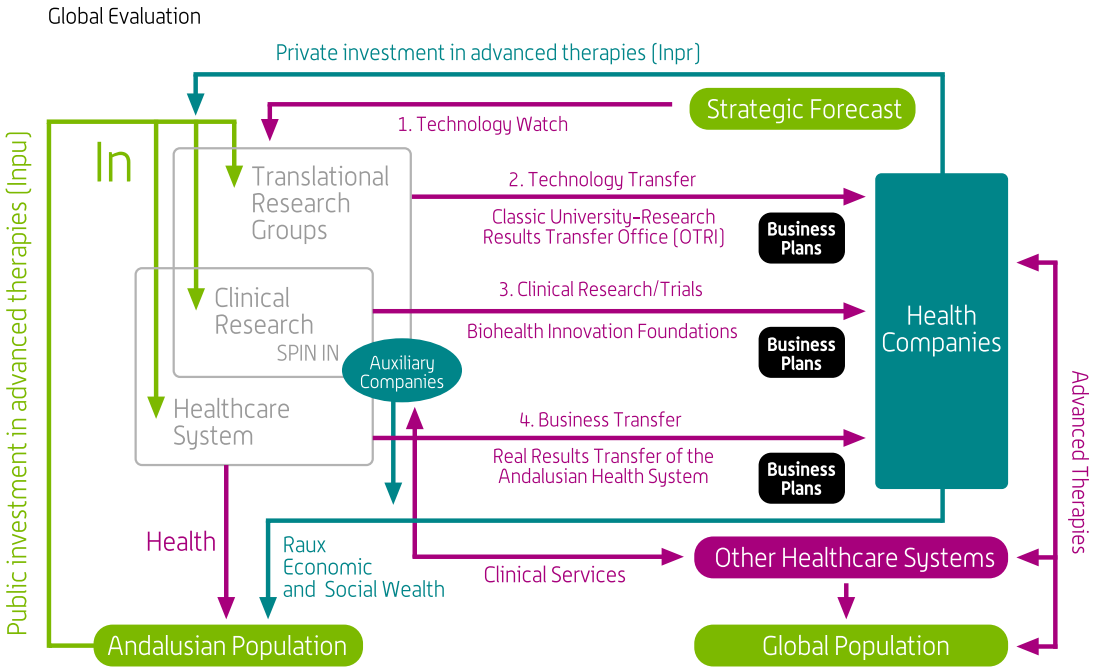
Taking a general, overall view, in the evolution from the initial to the final diagram, it can be seen that if the total investment level in the Initiative were maintained, public contribution would decrease, compensated by a new investment now from the private sector. In the case of the initial situation, the benefits from the results achieved would be felt in terms of the population's health, in addition to the generation of scientific knowledge, whilst in the final situation, new economic and social benefits would be achieved from auxiliary companies and health companies (indicating a return on the initial investment).

For these new companies, it would be necessary to consider business plans that would allow the creation and development of initiatives.

Process overview:

The process overview is set out below. This should be complemented by the development of a methodology that allows us to evaluate the results obtained from implementation of this proposal.

Ecomic Model: Evolution



2. Tools at the service of knowledge transfer and management

Boosting the generation of industrial property assets is not an end in itself but represents one of the key elements in helping to achieve suitable knowledge transfer.

The International Project Office and the OTT must play a fundamental role as necessary players for enhancing Industrial Property asset generation. But it is also important to achieve greater involvement of researchers in the transfer process.

The Andalusian Initiative for Advanced Therapies, in collaboration with the OTT, will prioritize a limited number of research lines that can be undertaken with the resources available at any given time. On an experimental basis, the development of the role of technology sponsor/observer will be tried out. The mission of these observers would be, among other duties, to interact with the research groups to study the evolution of their projects and in this way detect what milestones can generate Industrial Property Rights and immediately notify this to the OTT and to the Initiative. This, on the one hand, would benefit ongoing technology watch and, on the other, would enable the Initiative and the OTT to suitably manage the results and set milestones that increase the possibilities of the technology reaching society.

In order to select a limited series of research lines characterized by their high social and/or economic value to be prioritized by the Initiative, it is essential that thorough lists are prepared of those Andalusian research groups working in the areas of nanotechnology, genetics, biotechnology, etc., flagging up all those that are in national and international networks of excellence or have strong links with industry, and prioritizing those areas or research lines of excellence that have a high social and/or economic value, especially where their goal is the discovery of therapies for diseases that at present have no treatment.

It is essential that, in parallel to the creation of the technology sponsors/observers, ongoing training and awareness raising in the areas of industrial property, intellectual property and technological innovation are aimed at the different research groups of the different lines or research groups promoted by the Initiative. In addition a simple and clear transfer process for those results from I+D+i is required both for research groups and for the technology sponsors/observers who assist in the identification and transfer of the results.

On the other hand, the complexity and requirements on resources, time and effort of the licencing/assignment process would suggest that it is advisable to choose to carry out the licencing/assignment process only in those cases which may be successful. This will be done based on the prior evaluation of the selection process of the areas to be prioritized or the technology watch. Furthermore, it is

essential that the OTT has the active collaboration of the researchers, hence the importance of the role of the technology sponsors/observers in the effective transfer of this type of intangible assets.

Furthermore, the selection of the research lines to be prioritized must evaluate whether they are aligned with a clear business demand (in addition to the lines prioritized by virtue of their purely social criteria). This means selection should be based on a market study.

Furthermore, the technology sponsors/observers, in close collaboration with the OTT, should try to foster public-private collaborations, keeping the interest of both parties in mind, along with the effective translation of knowledge to society, in carrying out their ongoing technology watch brief.

However, the creation and consolidation of institutions that more efficiently and selectively manage the spin-off company creation process is required. Initially, this commitment may be preceded by public agencies that advise and even control this process, especially in the areas the Initiative wishes to develop. In this case, is important to maintain close collaboration with the IDEA agency.

These institutions must manage, at least in part, the Concept Testing Fund and decide when a technology must give rise to the emergence of a company or should be a candidate for the offer of a licence, in which case the OTT would be responsible for carrying it out. For this, they must have teams of professionals that:

1. Have experience in the technologies developed in the spin-off companies.
2. Offer support in the Business Development area.
3. Contribute to the strengthening of Industrial Property.
4. Have the capacity of finding other alternative funding channels.
5. Where applicable, advise on how to approach trials in order that the trial more closely adapts to clinical practice.
6. Are capable of giving the projects solidity and credibility in order to attract new sources of funding (e.g. Business Angels, Venture Capital, etc.)

7

ACTION PLAN

The uncertainties associated with the evolution of this field of research, its regulation and the possible risks and challenges that have to be faced, make it necessary to limit the Action Plan to a specific period of time in order to **lay the foundations** for its appropriate, smooth development

As has already been indicated in different sections of this document, the economic cycle for the development of new therapies, and for their access to the market, is clearly longer than the 6-year span of this Action Plan. However, the uncertainties associated with the evolution of this field of research, its regulation and the possible risks and challenges that have to be faced, make it necessary to limit the Action Plan to a specific period of time in order to lay the foundations for its appropriate, smooth development. However, future reviews of this plan with a much broader timeframe must follow in line with the economic cycle referred to above.

This Action Plan comprises activities which will be carried out throughout the 2010-2015 period and have been divided up into the following areas:

1) Strategic forecast
2) Knowledge generation and development of new therapies
3) Results transfer and application
4) Training
5) Communication actions undertaken by the Andalusian Initiative for Advanced Therapies

Some of the actions proposed refer to aspects included in more than one area, For this reason they are cited under more than one heading, but in each case other headings under which they are also cited are also indicated.

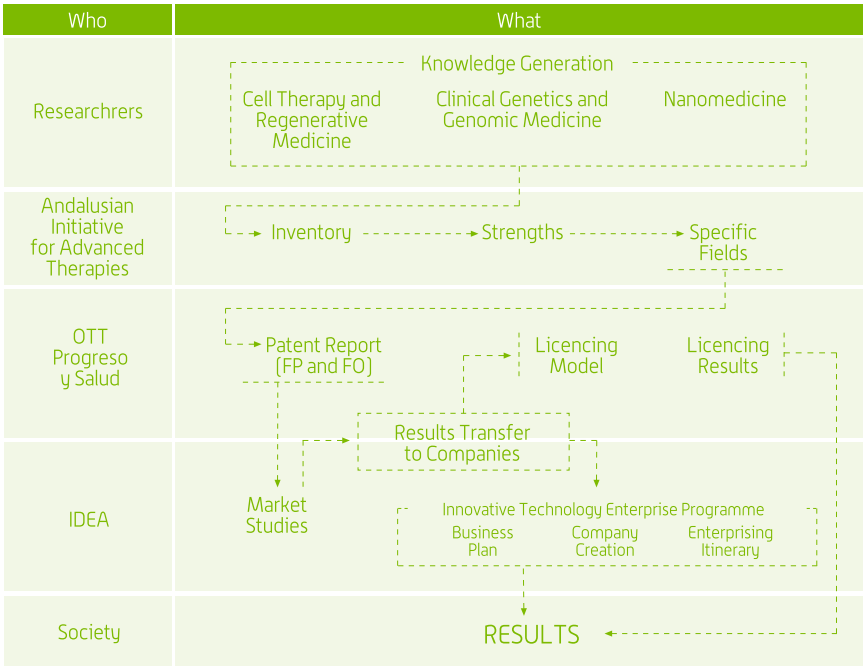
1. PRIORITIZATION AND STRATEGIC FORECAST

Strategic lines and actions

Line 1. The fundamental principle underpinning the feasibility of this initiative is the prioritization of those areas with a high potential for social and/or economic return on investment, whilst also offering a sufficient degree of scientific, technical and clinical development within Andalusia.

For the design of a coordinated strategy that covers the three Andalusian research programmes related to advanced therapies (Cell Therapy and Regenerative Medicine Programme, Clinical Genetics and Genomic Medicine Programme and Nanomedicine Programme) it will be necessary to know in advance what research resources are available in Andalusia. These include research centres, biobanks, universities, hospitals, health research institutes and human resources available in Andalusia, for basic, applied and clinical research, as well as other resources such as structures for the manufacturing of advanced therapy medicinal products, or GMP facilities and the companies active in this biotechnology and pharmaceutical area *(related to action 2.1)*.

The action proposal is summarized in the following diagram



1.1.

In order to identify those priority areas on which the Initiative's activity will focus during the 2010-2015 period, a **register of research groups** working within Andalusia will be prepared and a system will be designed to keep it updated. It must contain easily accessible information on the members forming each group, their main lines of research, the research production achieved in recent years and their relations with other regional, national and international groups. It must consider compatibility with the existing database of the Regional Ministry of Economy, Innovation and Science for the PAIDI (Andalusian Plan for Research, Development and Innovation) groups, and make use of the information which that database systematically collects. This research group register will be complemented by an **inventory of networks, centres and large teams** in the field of the advanced therapies research *(in relation to action 2.1)* and will be supported on a **web space** *(in relation to action 5.5)* which will facilitate collaboration between research groups and enhance translational research, enabling the researchers that access this inventory to propose potential regional, national and international collaborators. The idea is to develop a web space that encourages the notion that the framework of Andalusia is a fertile space for performing competitive translational research in the area of Advanced Therapies.

Who: Fundación Progreso y Salud (FPS) in collaboration with the Andalusian Initiative for Advanced Therapies and the Regional Ministry of Economy, Innovation and Science (CEIC)

When: 2 months (May-June 2010)

1.2.

Simultaneously, the **identification of those specific lines of knowledge that should be prioritized**[37] will commence. This will particularly consider those lines already highly developed and those very close or already in clinical research. However it will also bear in mind broader research lines that will make future development in advanced therapies possible.

Who: Directors or coordinators of the Cell Therapy and Regenerative Medicine, Clinical Genetics and Genomic Medicine and Nanomedicine programmes

When: 2 months (May-June 2010)

Notes

37. The areas initially proposed by way of guidance by the working groups are:

Cell Therapy and Regenerative Medicine:
- Cell therapy in cardiovascular diseases
- Cell therapy in neurodegenerative diseases
- Cell therapy in diabetes
- Cell therapy in hepatic diseases and chronic inflammatory digestive diseases
- Tissue engineering, especially in the area of dermatology, urology, ophthalmology and articular pathology, including intensive tissue treatments and combinations.
- Stem cells and cancer

Clinical Genetics and Genomic Medicine:
- Studies on the genetic basis and genomic epidemiology of cancer
- Studies on the genetic basis and genomic epidemiology of rare diseases
- Genetic variability associated with neurodegenerative, heart and autoimmune diseases
- Gene therapy in rare diseases and cancer

Nanomedicine
- Synthesis and characterization of nanoparticles aimed at in vitro nanodiagnosis and smart-delivery applications in neurodegenerative diseases, immunotherapy and cancer
- Nanosystems for gene therapy and studies of gene function in neurodegenerative diseases and cancer.
- Micro- and nano-fluidic applications for the development of lab-on- a-chip

1.3.

After the creation of a group register and an initial identification of possible lines to prioritize, the **External Advisory Committee of the Andalusian Initiative for Advanced Therapies**[38] will then use that information to make a **scientific-technical assessment. This assessment will** enable the **selection of those lines to prioritize**, as well as their **classification** into short-term lines (already in clinical research or close to it) and medium/long-term lines. It will also incorporate the relevant information to justify their selection and time frame into that classification.

Who: External Advisory Committee of the Andalusian Initiative for Advanced Therapies

When: 2 months (July and September 2010)

1.4.

Review of the classification of the short-term and medium/long-term lines prioritized with the help of the information prepared. The first block will include all information on those specific lines that are either in clinical research or close to it and where precise information is available on their development for use. A second block will contain all information relating to the other lines to be prioritized (medium/long-term) with the aim of guaranteeing future results within certain areas of special interest.

Who: OTT of SSPA, Fundación Progreso y Salud

When: October 2010

The prioritization process is concluded once the Fredom to Operate (FTO) of the initially prioritized lines have been analysed. These actions are included in strategic lines 10 and 11 of this document, regarding protection and results transfer.

1.5.

Establishment of a **"New Therapy Trends Observatory"**, via a functional structure, with the aim of capturing up-to-date information on emerging trends and strategic forecast tools. Based on this, it will be possible to propose updates to the research lines initially prioritized in the Andalusian Initiative for Advanced Therapies' strategy in the areas of Cell Therapy and Regenerative Medicine, Clinical Genetics and Genomic Medicine and Nanomedicine. This observatory should generate annual working documents that are public and will have the collaboration of the Technical Committee for Clinical Research *(related to action 7.4)* and the External Scientific Advisory Committee of the Andalusian Initiative for Advanced Therapies *(related to action 1.3)*.

Who: Regional Ministry of Health in collaboration with the Andalusian Initiative for Advanced Therapies

When: 2010-2015.

1.6.

Establishing a working group to analyse the **impact** that the newly developed therapies may have on **the Public Health System** and its organisation.

Who: Andalusian Initiative for Advanced Therapies

When: 2011-2015.

Notes

38. This Committee will be selected by the Governing Committee of the Initiative at the proposal of the Directors or coordinators of the Cell Therapy and Regenerative Medicine, Clinical Genetics and Genomic Medicine and Nanomedicine programmes, and the Initiative's Management. It will be composed of a multidisciplinary panel of Spanish and international experts, incorporating leading basic and clinical researchers in these areas of research, experts in results transfer, venture capital and capital from the business sector. This Committee will take part in the biennial evaluation of the Action Plan (see chapter VIII).

2. KNOWLEDGE GENERATION AND DEVELOPMENT OF NEW THERAPIES

Within the framework of the three research programmes: Cell Therapy and Regenerative Medicine, Clinical Analysis and Genomic Medicine and Nanomedicine, the Andalusian Initiative for Advanced Therapies will promote those results that are oriented toward the fostering of the synergies between the different areas of knowledge and between the area of basic, applied and clinical research, ultimately favouring translational research."

Servicio Andaluz de Salud. Consejería de Salud. Junta de Andalucía.

Strategic objectives:

- Equipping and adapting infrastructures to the requirements of biomedical research and the manufacturing of advanced therapies, promoting the efficiency of their use.
- Providing research staff to increase the critical mass of researchers in the field of advanced therapies as well as technical staff to carry out the manufacturing of medicinal products for human use under appropriate conditions.
- Favouring synergies and collaborative multidisciplinary research in advanced therapies, with a translational orientation that contributes to clinical innovation.
- Promoting biomedical research of excellence in areas of maximum interest, together with highly creative unconventional research.
- Fostering high-quality clinical trials in areas of maximum interest and giving support for their execution as well as for their compliance with the regulatory framework, organization of quality controls, suitable characterization and development of products and improved production systems.
- Encouraging the captation of public and private financial resources to develop research projects in Advanced therapies, as well as for the funding of necessary new infrastructures.

Strategic lines and actions

Line 2. Drawing up an inventory of the infrastructures and equipment available in Andalusia, for the rational and efficient use of resources.

2.1.

Creating a **Network of Material Resources for Research**, incorporating the facilities and physical and virtual resources which are shared between the different agents of the Andalusian Knowledge System. This network of resources will complement the inventory of groups *(related to action 1.1)*. The objective is to enable a **shared use of existing resources**, common use and integration of the facilities, as well as detecting those infrastructures and platforms that are necessary but not available so that they can be subsequently funded.

Who: Fundación Progreso y Salud (FPS) in collaboration with the Andalusian Initiative for Advanced Therapies and the Regional Ministry of Economy, Innovation and Science (CEIC)

When: May-September 2010

2.2.

Creating a **directory** which will provide information concerning all the calls for subsidies for infrastructures at a regional, national and international level, in order to improve efficacy and efficiency when applying.

Who: Fundación Progreso y Salud (FPS) in collaboration with the Andalusian Initiative for Advanced Therapies and the Regional Ministry of Economy, Innovation and Science (CEIC)

When: May-September 2010

Line 3. Providing Andalusia with the necessary infrastructures and equipment to develop and give support to basic and clinical research in advanced therapies, focusing on the effectiveness of their use.

3.1.

Completing the construction and fitting out of benchmark **monographic research centres** for those research programmes related to advanced therapies.To CABIMER (Cell Therapy and Regenerative Medicine Programme) we will be able to add GENYO (Clinical Genetics and Genomic Medicine Programme) and BIONAND (Nanomedicine Programme), once their construction is complete and they have been fitted out. These benchmark centres for research programmes related to advanced therapies will collaborate with the research carried out in these fields by other non-monographic research centres, research institutes and health centres.

Who: Regional Ministry of Health and Regional Ministry of Economy, Innovation and Science (CEIC) in collaboration with the participating Universities and Companies.

When: 2010

3.2.

Creating the **biobanks** necessary to give support to the research in advanced therapies, such as the DNA bank or possibly other banks of some biological fluids. They will form the Andalusian Biobank Network together with the biobanks already in place.

Who: Regional Ministry of Health.

When: 2nd half of 2010

3.3.

Building **special infrastructures** to promote research in emerging research areas related to innovative techniques for cell reprogramming and mass sequencing of DNA samples.

Who: Regional Ministry of Health.

When: 2010-2011

3.4.

Adapting the **network of pharmaceutical laboratories** for the production of advanced therapy medicinal products (GMP laboratories) to the manufacturing requirements of products being researched for their clinical application, improving the efficiency of their use through an **organization** system and a general management model, that enhances its **self-funding**.

There are currently eight **Cell Therapy** Manufacturing Units in our region, equipped with a total of twelve clean rooms in different phases of construction for the production of cells for Clinical Research. One of these units is located in a mixed research centre and the seven remaining ones in healthcare centres belonging to the Andalusian Public Health System (of which four are located inside tissue banks, favouring their possible use in tissue engineering developments). In principle, these infrastructures should be sufficient to cover the initial phases of the cell therapy clinical trials to be carried out in Andalusia, although it is not possible at this time to accurately predict the medium-term production requirements. In order to get maximum joint return on the overall cell production capacity in the total number of manufacturing units, coordination mechanisms will be set out by the Initiative's Executive Director for those units of the Andalusian Public Health System, in collaboration with their technical directors. An organization and management model will be designed to enhance its self-funding *(related to Line 9)*, and annual meetings will be held to assess cell production requirements as well as production capacities for each of the Units.

It is important to bear in mind that with the current production systems the Cell Therapy manufacturing units can only cover the cell production requirements for phase I and II clinical trials, in the best case scenario. The future introduction of **Phase III trials** may well make it necessary to seek agreements with companies or create spin-offs, To reach these agreements it will be essential to have suitable knowledge transfer mechanisms for this purpose *(related to lines 10 and 11)*.

On the other hand, given the rate of scientific progress in **cell reprogramming** and in the fields of **gene therapy** and **nanomedicine**, it would be necessary to assess the opportunity of creating new production infrastructures adapted to research products in these areas. The results of the strategic forecast and technology watch activities, together with the market studies *(in relation to actions 1.5, 10.2, 11.1 and 11.3)* will establish the possible convenience of creating new infrastructures.

Who: Andalusian Initiative for Advanced Therapies

When: 2010-2015

Line 4. **Progressively increasing the critical mass of researchers in the field of advanced therapies, attracting talent, incorporating technicians and favouring the incorporation of young researchers into the system in line with the framework for the future Andalusian Programme for the Development of Human Capital in Biomedical Research.**

4.1.

Promoting research in Cell Therapy and Regenerative Medicine, Clinical Genetics and Genomic Medicine and Nanomedicine by offering job opportunities in centres related to those areas of research for the **Sara Borrel** and **Miguel Servet** programmes of the Carlos III Health Institute and **Ramón y Cajal** and **Juan del la Cierva** of the Ministry of Science and Innovation.

Who: Regional Ministry of Health and/or Regional Ministry of Economy, Innovation and Science

When: 2010-2015

4.2.

Implementing a **specific contract stability programme** aimed at those researchers in the prioritized areas who have previously enjoyed a competitive stabilization contract, such as the aforementioned. They would be incorporated in health centres and public research centres dependent on the Andalusian Public Health System or associated with the Regional Ministry of Health.

Who: Regional Ministry of Health and/or Regional Ministry of Economy, Innovation and Science

When: 2010-2015

4.3.

Implementing a programme that facilitates the **incorporation of researchers of recognised international prestige** in the thematic areas prioritized by the Inititative. The programme will reflect the demands of the research centres and institutes of the Andalusian Public Health System. Respecting at all times the principle of scientific excellence, it will encourage, insofar as possible, the **return of Andalusian researchers** who are working as such abroad. Each researcher who joins will have laboratory space, human resources and equipment, in addition to initial financial support to be able to set the project to be executed in motion. The follow-up procedure of the activities performed by the Principal Investigators will be defined. They must incorporate teaching as an element of their activity.

Who: Regional Ministry of Health and/or Regional Ministry of Economy, Innovation and Science

When: 2010-2015

4.4.

Establishing a specific subsidy programme to **recruit support technicians** for research in the areas of innovation prioritized in the Programme and **post-doctoral researchers**, preferably in health centres and public research centres associated to the Andalusian Public Health System.

Who: Regional Ministry of Health and/or Regional Ministry of Economy, Innovation and Science

When: 2010-2015

4.5. ————

Promoting, through the Regional Ministry of Health and within the context of the Andalusian Public Health System, the compatibility of healthcare activity with research activity, through the development of new elements to be established within the **Andalusian Programme for Development of Human Capital in Biomedical research**.

Who: Regional Ministry of Health and/or Regional Ministry of Economy, Innovation and Science

When: 2010-2015

4.6. ————

Favouring research in advanced therapies within **research activities** carried out by resident physicians and students of medicine and other healthcare professions and disciplines found in the Andalusian Public Health System. The objective is twofold: a) they enrich the clinical and translational vision of research and b) they are the basis of future components of research groups with a healthcare profile but with a real vision of the research procedure.

Who: Regional Ministry of Health and/or Regional Ministry of Economy, Innovation and Science

When: 2010-2015

4.7. ————

Promoting the incorporation of **post-doctoral students** in research lines in advanced therapies using subsidies from the different government bodies.

Who: Regional Ministry of Health and/or Regional Ministry of Economy, Innovation and Science

When: 2010-2015

4.8. ————

Guaranteeing the numbers of staff necessary to run **public GMP laboratories** in Andalusia related to the Andalusian Initiative for Advanced Therapies for the manufacturing of medicinal products.

Who: Regional Ministry of Health

When: 2010-2015

Line 5. **Encouraging the interdisciplinary nature and synergies between the knowledge areas of the 3 Andalusian research programmes related to advanced therapies and between the basic and clinical research teams to enable the translational development of the strategic lines which have been set out.**

5.1. ————

Organizing a **regular seminar** inviting basic and clinical researchers related to the three areas included in the Initiative (Cell Therapy and Regenerative Medicine, Clinical Genetics and Genomic Medicine, and Nanomedicine) and with the participation of researchers from the research centres and institutes in addition to researchers and clinical practitioners assigned to health centres in the Andalusian Public Health System. In this way results can be disseminated between the R&D&i agents of the Andalusian Public Health System and other agents of the Science-Technology-Enterprise system, and cooperation between groups with similar scientific-therapeutic interests can be promoted.

Who: Andalusian Initiative for Advanced Therapies together with Fundación Progreso y Salud

When: 2011-2015

5.2.

Promoting, by means of positive discrimination in all research support measures, the development of **coordinated and multidisciplinary research projects** with the priority objective of enhancing translation into **advanced therapies**.

Who: Regional Ministry of Health and Regional Ministry of Economy, Innovation and Science

When: 2011-2015

5.3.

Facilitating the creation of suitable spaces within the health institutions where **clinical interests and research and laboratory interests can come together**. This makes it possible to develop projects aimed at verifying hypotheses and/or generating knowledge and applications derived from solid clinical observation.This also facilitates learning and makes it possible to share knowledge with units which are starting clinical research activities in this field.

Who: Regional Ministry of Health

When: 2010-2015

5.4.

Communicating the possible start-up of new clinical trials to those hospitals which, it is considered, may be interested in participating in and disseminating the information regarding those clinical trials which, at any one time, are in the patient recruitment phase across all the Andalusian Public Health System centres. This will allow patients from the entire region access to trials being carried out in any of the hospitals there *(related to actions 7.3 and 7.6)*.

Who: Andalusian Initiative for Advanced Therapies

When: 2nd half of 2010

5.5.

Creating a **web space** *(related to action 1.1)* which facilitates collaboration between research groups and enhances translational research, enabling researchers accessing this inventory, to nominate potential regional, national and international collaborators. The idea is to develop a web space to reinforce Andalusia's emergent brand as a fertile region for performing competitive translational research in the area of Advanced Therapies.

Who: Fundación Progreso y Salud in collaboration with the Andalusian Initiative for Advanced Therapies

When: 2nd half of 2010

Line 6. **Promoting biomedical research of excellence in areas of maximum interest, together with highly creative unconventional research.**

6.1.

Establishing **mechanisms to evaluate** scientific and innovative capacity, disseminating the results among the research groups and promoting the definition and introduction of selection criteria and the length of stay of researchers in research centres.

Who: Regional Ministry of Health and Regional Ministry of Economy, Innovation and Science

When: 2010-2015

6.2.

Identifying mechanisms to stimulate and support **highly creative unconventional research projects**.

Who: Regional Ministry of Health and Regional Ministry of Economy, Innovation and Science

When: 2011-2015

Line 7. Promoting quality clinical trials in areas of maximum interest, keeping equal access criteria for patients firmly in mind

7.1.

Setting up **mechanisms of communication and coordination** with the Directors of the Regional Ministry of Health Plans, making it possible to identify areas of maximum interest, from a healthcare standpoint, in which implementation of clinical trials can be fostered *(related to action 7.4)*.

Who: Andalusian Initiative for Advanced Therapies

When: 2010-2015

7.2.

Promoting **preclinical research** in areas of maximum interest through mechanisms of positive discrimination in research support measures and advice to researchers regarding the requirements demanded by the regulatory agencies in order for this research to be translated into clinical practice. Special attention will be paid to the toxicological studies, which may need the collaboration of private institutions specialized in this kind of study. Likewise, a shared risk model will be worked on right from preclinical phases to the search for partners in the private sector.

Who: Andalusian Initiative for Advanced Therapies

When: 2010-2015

7.3.

Facilitating web-based communication between research groups and the Initiative, on new Clinical Trials projects. Proposals for development of clinical trials in Advanced Therapies come, in most cases, from clinical research groups in the Andalusian Public Health System or from basic research groups where the development levels of the experimental knowledge and in animal models may justify the start of a phase I trial. In this sense, it is proposed to **set up a space within the Initiative website** that serves as a permanent and dynamic communication channel where **both basic and clinical researchers** can communicate their clinical trials projects in Advanced Therapies to the Inititative. This page will be in connection with the communication web space included in action 5.4. The Initiative's website will host a **proposal model** that will include at least a summary of the clinical trial proposed, phase and its design proposal, the clinical objectives, the assessment of the clinical trial's safety, a bibliographic review, as well as the technical and human resources available to perform the research *(related to action 5.4)*.

Who: Andalusian Initiative for Advanced Therapies in collaboration with Fundación Progreso y Salud

When: 2nd half of 2010

7.4.

Creating a **Technical Committee for Clinical Research** coordinated by the Initiative that flexibly and operationally evaluates the relevance and suitability of the clinical research proposed. A **Safety Commission** will be established in this committee to analyse any incidents that may affect patient safety and any serious and unexpected adverse events that may arise in the course of the advanced therapy clinical trials promoted by the Andalusian Initiative for Advanced Therapies.

Who: Andalusian Initiative for Advanced Therapies

When: May-June 2010

7.5.

Establishing scientific-technical criteria to consider a clinical trial proposal as suitable, as well as criteria for a centre's participation in a clinical trials and the criteria for its continuity.

Who: Technical Committee for Clinical Research coordinated by the Andalusian Initiative for Advanced Therapies

When: July-September 2010

7.6.

Assessing compliance with criteria for the implementation of a clinical trial, for the participation of the applicant centres and their continuity. If **the Initiative**, through its Technical Committee for Clinical Research, considers it to be initially pertinent to perform the proposed trial, from that time on **it will take charge and advise**, together with the collaboration of the Technical Committee for Clinical Research, the research group and the hospitals considered suitable for participation with regard to those aspects related to fund raising that enable the development of the trial to go ahead, as well as in the necessary regulatory and authorization aspects *(related to actions 7.1, 8.1 and 8.4)*.

Who: Technical Committee for Clinical Research coordinated by the Andalusian Initiative for Advanced Therapies

When: October 2010-2015

7.7.

Analysing the feasibility and relevance of setting out mechanisms that promote **equal access to clinical trials** especially for patients affected by pathologies with no therapeutic alternatives.

Who: Regional Ethics and Health Research Committee

When: 2nd half of 2010-1st half of 2011

7.8.

Encouraging the Regional Ministry of Health to revise the annual call **for funding** of research projects to include the **special characteristics of clinical trials in advanced therapies**, so that the execution times are in line with the authorization periods and that it allows for the compatibility of researchers who are benefitting from subsidies received in previous calls.

Who: Andalusian Initiative for Advanced Therapies and the Regional Ministry of Health

When: 2011-2015

Line 8. **Giving support to clinical research in advanced therapies and the manufacturing of products in research.**

8.1.

Giving **logistics support** for the carrying out of clinical trials, acting as their sponsor and giving administrative support in processing the trial authorization by the AEMPS and Committees involved.

Who: Andalusian Initiative for Advanced Therapies in collaboration with Fundación Progreso y Salud and the Andalusian Health Service

When: 2010-2015

8.2.

Facilitating coordination between researchers participating in clinical trials concerning the application of homogeneous criteria, by creating a special **forum** for the use restricted to these researchers within the website of the Andalusian Initiative for Advanced Therapies.

Who: Andalusian Initiative for Advanced Therapies in collaboration with Fundación Progreso y Salud

When: 2010 - 2015

8.3.

Providing support in the search for the **material resources** required to manufacture the medicinal products and to carry out clinical trials *(related to Line 9)*. The expenses due to hospitalization, diagnostic tests and treatments dispensed, aside from the product undergoing research in the patients participating in non-commercial clinical trials promoted by the Initiative, will be assumed by the hospitals participating in the trials, so that the sponsor will establish contracts with economic reports without costs. Agreements will be promoted with CAIBER to collaborate in specific aspects such as clinical trial monitoring and design, as well as result analysis.

Who: Regional Ministry of Health through the Andalusian Initiative for Advanced Therapies, Fundación Progreso y Salud and the Andalusian Health Service

When: 2010-2015

8.4.

Giving advice to comply with the **regulatory framework**, through the Initiative's Medical and Regulatory Affairs Coordinator, the Initiative's Head of Clinical Trials and the FPS Legal Advice Service, which will act as sponsor of all Trials, both for the implementation of clinical trials and for the manufacturing authorization of trial drugs and medicinal products of demonstrated efficacy, or for them to be incorporated in the National Health System Services Portfolio.

Who: Andalusian Initiative for Advanced Therapies and Fundación Progreso y Salud

When: 2010-2015

8.5.

Giving support to the trial drug manufacturing laboratories to organize **manufacturing process quality controls**, through the Initiative's Head of Quality and Accreditation, with the collaboration of the Technical Directors of the advanced therapies pharmaceutical laboratories assigned to the Andalusian Initiative for Advanced Therapies, thus creating a benchmark laboratory.

Who: Andalusian Initiative for Advanced Therapies

When: 2010-2015

8.6.

Giving guidance on **product characterization and development**. This aspect is vital and collaboration between the Technical Directors and the Head of Production of the different pharmaceutical laboratories is, therefore, essential. The Technical Directors will meet periodically in order to agree on trial product characterization protocols and will have the collaboration of the Initiative's Evaluation and Strategic Forecast Manager as well as external advisors that may be recruited depending on requirements.

Who: Andalusian Initiative for Advanced Therapies and Technical Directors of pharmaceutical laboratories assigned to the Initiative

When: 2010-2015

8.7.

Improving **production systems** to allow greater standardization in the manufacturing of medicinal products, process automation and production scaling, as well as the progressive elimination of products of animal origin in the production process. The Technical Directors will meet periodically in order to agree on production systems improvements and will have the collaboration of the Initiative's Head of Quality and Accreditation and the Initiative's Evaluation and Strategic Forecast Manager as well as external advisors that may be recruited, depending on requirements.

Who: Andalusian Initiative for Advanced Therapies and Technical Directors of pharmaceutical laboratories assigned to the Initiative

When: 2010-2015

Line 9. **Developing an active policy to seek public and private funding for projects undertaken within the framework of the Initiative.**

9.1.

Being in permanent contact with the public and private research **funding areas** to search for R&D&i lines of finance in advanced therapies.

Who: Research management agencies of the Andalusian Public Health System, coordinated by Fundación Progreso y Salud in collaboration with the International Project Office of the Andalusian Public Health System and the Andalusian Initiative for Advanced Therapies

When: 2010-2015

9.2.

Making a personalized **dissemination** of the different international, national and regional **calls** for public and private subsidies that are of interest for research in the areas of the Andalusian Initiative for Advanced Therapies. The dissemination will be made to centres and researchers who have previously requested to be included on the distribution lists.

Who: Research management agencies of the Andalusian Public Health System, coordinated by Fundación Progreso y Salud in collaboration with the International Project Office of the Andalusian Public Health System and the Andalusian Initiative for Advanced Therapies

When: 2010-2015

9.3.

Promoting access to **European and International funding**, disclosing the areas of interest of the Andalusian Public Health System to the financing agencies and possible partners and highlighting the R&D&i developed in the different areas of innovation prioritized by the Andalusian Initiative for Advanced Therapies.

Who: Research management agencies of the Andalusian Public Health System, coordinated by Fundación Progreso y Salud in collaboration with the International Project Office of the Andalusian Public Health System and the Andalusian Initiative for Advanced Therapies

When: 2010-2015

9.4.

Establishing alternative funding channels with **private companies** through fund-raising initiatives.

Who: Research management agencies of the Andalusian Public Health System, coordinated by Fundación Progreso y Salud in collaboration with the International Project Office of the Andalusian Public Health System and the Andalusian Initiative for Advanced Therapies

When: 2010-2015

3. RESULTS TRANSFER AND APPLICATION

Strategic objectives:

- Boosting the generation of industrial property assets **that enable** suitable knowledge transfer:

  a. Slowing down the continuous loss in value of results capable of generating industrial property rights, due to previous communications.

  b. Establishing comfortable, easy and safe channels for the communication of results capable of industrial property rights, thus allowing the analysis of a greater number of research results.

  c. Providing tools that make it possible to select and screen those R&D&i results of greatest value with a view to their possible translation to society.

  d. Generating greater involvement of researchers in the transfer process.

  e. Promoting public-private collaboration agreements.

- Fostering the industrial fabric to which the technologies or know-how derived from the PRB can be transferred, whether by licences, collaboration agreements, creation of spin-off companies or any other type of transfer.

- Boosting the development of our own transfer model that leads to value creation promoting open public-private association models, from the very first phases of clinical research, that also include reverse transfer formulas, opening collaboration channels with the business sector and developing market niches in auxiliary services for the research.

- Facilitating the incorporation of those new therapies developed both inside and outside Andalusia in the Public Health System, after evaluating their relevance.

Strategic lines and actions

Line 10. **Promoting mechanisms for the protection and transfer of the results of those lines of short-term research which have been selected by the Andalusian Initiative for Advanced Therapies and which facilitate future clinical application.**

10.1. ————

Analysing the "Freedom to Operate" (FTO). This make it possible to know if the technology is already protected or if it can be protected, in what way and with what scope and what the obstacles are that may be encountered in the industrial property area when marketing or implementing the use of this technology. These types of studies (for a maximum of 15 lines) will end with very clear conclusions enabling fast decision-making.

Who: OTT of SSPA, Fundación Progreso y Salud

When: 4 months (October 2010-January 2011)

10.2. ————

Performing **market studies**. After carrying out the "Freedom to Operate" analysis, thorough market studies will be prepared on these lines (for a maximum of 15 lines) including both aspects relating to the possibilities of their technological development and the real possibility of their reaching the market, i.e. that they can be transformed into a product which the end customer wants to buy. The market studies must be prepared by professionals knowledgeable about the technology, but, above all, capable of performing a serious and rigorous market research for those results. The market study must conclude with specific milestones in preclinical or clinical development associated with its anticipated market niche.

Who: IDEA agency (with the collaboration of the OTT-SSPA, Fundación Progreso y Salud, in identification of the professional profiles).

When: 3 months (February-April 2011).

10.3. ————

Defining the **prioritization and transfer mechanisms**. From the scientific-technical information, the analysis of the Freedom to Operate and the market studies, the short-term possibilities of each line producing a social or economic return will be determined (these might include the possibility that the results may give rise to the creation of a company, that they may be licensed or that their market possibilities are very uncertain). Additionally, these studies will establish a series of milestones that must be achieved throughout the project and which must serve as a guide to set the objectives of the sponsoring agent. The following decisions will be taken as a result:

a) Lines to prioritize within the lines of excellence in the short-term.

b) Creating and piloting the role of **technology sponsor/observer**. These people will have the basic mission of managing each one of the short-term lines in accordance with the milestones set and with the contingencies that may arise.

c) Form of prioritizing the different areas selected: funding, support, etc.

It is estimated that implementation of the short-term lines will have been completed by May 2011 and from that time on they will be managed, in accordance with the milestones set, by the technology sponsors/observers.

Who: Andalusian Initiative for Advanced Therapies with the collaboration of the External Advisory Committee and Governing Committee.

When: 2 months (May-June 2011).

Line 11. **Promoting mechanisms for the protection and transfer of the results of the medium/long-term research lines, selected by the Andalusian Initiative for Advanced Therapies, and which facilitate future clinical application**

11.1. ————

Performing **market studies**.The medium/long term lines are characterized by the fact that the therapy in question is at a low level of development and, therefore, they lack sufficient information on the type of product or method to be used or use to be made of this therapy. This situation does not allow the analysis of the Freedom to Operate. Therefore, market studies will be prepared on these lines exclusively with the scientific-technical information (for a maximum of 15 lines). These studies will include aspects of their own possibilities for technological development as well as of the real possibility of their reaching the market, i.e. whether they may transform into a product that a customer wants to buy.

Who: IDEA agency (with the collaboration of the OTT-SSPA, Fundación Progreso y Salud, in identification of the professional profiles).

When: 4 months (October 2010-January 2011).

11.2.

Defining the **prioritization mechanisms**. The following decisions shall be taken from the scientific-technical information and the market studies:

a) Lines to prioritize within the lines of excellence in the medium/long-term.

b) Creating and piloting the role of **technology sponsor/observer**. These people will have the basic mission of managing each one of the medium/long-term lines basically in terms of **technology watch**.

c) Form of prioritizing the different areas selected: funding, support etc.

d) Establishing a **tender procedure** to select those entities that may be used to perform the patentability or Freedom to operate analysis.

It is estimated that the medium/long-term lines will have been completed in March 2011 and from that time on, the work of the observers/ technology sponsors will be vital.

Who: Andalusian Initiative for Advanced Therapies with the collaboration of the External Advisory Committee and Governing Committee. The FPS will collaborate in the tender procedure or negotiation of agreements with Fundación Genoma España

When: 3 months (February-April 2011).

11.3.

Carrying out ongoing **technology watch** of the medium/long-term lines by the **technology sponsors/observers** who should perform the following functions:

a) Monitor each of the groups that research each of the medium/long-term lines.

b) Analyse the market to determine possibilities for public-private collaborations.

c) Manage the research results. In this sense, the sponsor has the obligation of immediately notifying the competent OTT of the results as soon as they are obtained, and if there is any doubts about who is the competent OTT, the FPS' OTT puts itself forward to advise the sponsors.

Who: Technology sponsors/observers in collaboration with the OTT and FPS

When: 2011-2015

11.4.

Determining, via the competent OTT, if the results provided by the technology sponsors/observers can be protected and, if so, select the best **form of protection**. To carry out this study, the OTT must use one of the agencies selected by the Initiative. This information should be provided to the Initiative once it has been obtained by the technology sponsors/observers.

Who: The competent OTT in collaboration with agencies selected by tender procedure

When: 2011-2015

11.5.

Deciding the suitability of carrying out additional studies, in the light of the information obtained with regard to the possibility of protection. These studies include: analysis of future developments of the results obtained in order to take them to clinical practice, setting a series of milestones to be achieved, based on clinical and economic/social criteria, and Freedom to Operate studies, to thus be able to take the decision to go ahead with that line of research based on its possible social and/or economic return.

Who: Andalusian Initiative for Advanced Therapies in collaboration with the OTT-SSPA, Fundación Progreso y Salud

When: 2011-2015

11.6.

Providing the IDEA agency with the information, in those cases in which the Initiative decides to go ahead with preparation of the previous analysis, so that it can execute it, through third parties with the capacity to do this. The same will happen with the Freedom to Operate, of which the competent OTT will take charge. In any case, if the Initiative, with or without the previous Freedom to Operate analysis or study, decides to go ahead with the line of research, it will, in any case, set a series of milestones, based on results, to be achieved by the technology sponsors/observers in that specific research line. (It is convenient to perform the technology development analysis to set these milestones and in this way correctly manage the results based on milestones that can be quantified).

Who: IDEA Agency and the OTT in collaboration with agencies selected by tender procedure

When: 2011-2015

The rules of the tender procedure will specify the prices to be paid for the study. However, it may be appropriate to reach an agreement with Fundación Genoma España since it is already paying for this type of study and, therefore, not allocate any further public funds to these purposes.

Line 12. Promoting returns in health and socio-economic terms by encouraging the licensing of protected knowledge or company creation.

12.1.

Disseminating the new therapies in the widest possible sense, along with their procedures and possible technologies.

Who: Andalusian Initiative for Advanced Therapies, Fundación Progreso y Salud and the Andalusian Health Service

When: 2011-2015

12.2.

Incorporating the new therapies in the Andalusian Public Health System, when relevant, and designing a coordination plan for this.

Who: Andalusian Initiative for Advanced Therapies, Fundación Progreso y Salud and the Andalusian Health Service

When: 2011-2015

Within those prioritized short or medium/long term lines that may also give rise to a possible economic return, the technology sponsors/observers will have technology licensing or company creation marked as one of their milestones. In this sense, it is important that the competent OTT collaborates with the agent. In any case, the OTT of Fundación Progreso y Salud makes the services of its Identification and Translation of Intangible Assets Department available to the Initiative, to successfully promote the return on investment, both in terms of health and the socio-economic aspects of the knowledge protected. For this purpose, this department will analyse the market studies, Freedom to Operate reports and patentability reports of each research project, and depending on the arguments put forward, will determine the strategy to follow, choosing an operating licence for the use of technology or creation of a company.

If it is decided to licence the technology to third parties, the following specific actions will be performed:

12.3.

Identification of companies that may be interested on a regional, national and international basis.

Who: Fundación Progreso y Salud and the Andalusian Initiative for Advanced Therapies

When: 2011-2015

12.4.

Preparation of technology offers for both passive and active approaches to these companies. In the case of a passive approach, the technology offer will be posted on the main websites for technology supply and demand. In the active approach, companies will be directly contacted and a customised technology offer will be put forward to them.

Who: Fundación Progreso y Salud and the Andalusian Initiative for Advanced Therapies

When: 2011-2015

12.5.

Contact with these companies to try to establish collaboration and/or technology user licence.

Who: Fundación Progreso y Salud and the Andalusian Initiative for Advanced Therapies

When: 2011-2015

12.6.

The preparation of all relevant legal documents, through the legal department of Fundación Progreso y Salud, to enable those agreements to be reached.

Who: Fundación Progreso y Salud and the Andalusian Initiative for Advanced Therapies

When: 2011-2015

In the case of opting for company creation, the following specific actions will be performed:

12.7.

Finding business incubators. Thus, a small inventory will be made incorporating the characteristics and services offered.

Who: The IDEA agency of the Regional Ministry of Economy, Innovation and Science which has a series of tools at its disposal, namely: Business Plan, Company Establishment, Business Coaching and the Enterprising Start-up Guides in collaboration with the OTT-SSPA of Fundación Progreso y Salud and the Andalusian Initiative for Advanced Therapies

When: 2011-2015

12.8.

Looking for public-private funding channels.

Who: The IDEA agency of the Regional Ministry of Economy, Innovation and Science which has a series of tools at its disposal, namely: Business Plan, Company Establishment, Business Coaching and the Enterprising Start-up Guides in collaboration with the OTT-SSPA of Fundación Progreso y Salud and the Andalusian Initiative for Advanced Therapies

When: 2011-2015

12.9.

Identifying managers for these companies.

Who: The IDEA agency of the Regional Ministry of Economy, Innovation and Science which has a series of tools at its disposal, namely: Business Plan, Company Establishment, Business Coaching and the Enterprising Start-up Guides in collaboration with the OTT-SSPA of Fundación Progreso y Salud and the Andalusian Initiative for Advanced Therapies

When: 2011-2015

4. TRAINING

Strategic objectives:

- Training professionals in the areas of manufacturing and quality control of Advanced Therapy medicinal products.
- Facilitating training of researchers in Advanced Therapies.
- Favouring the mobility of researchers.
- Providing researchers with management tools.

Strategic lines and actions

Line 13. **Training professionals to manufacture drugs for use in Advanced Therapies and setting clinical trials in motion with these therapies:**

- Technical Directors of Advanced Therapy pharmaceutical laboratories
- Production, quality control and quality assurance managers
- Lab technicians in pharmaceutical production and quality control
- Clinics wishing to promote Advanced Therapy clinical trials

13.1.

Designing a modular **training programme** to meet the training requirements of all the above professionals, and with the clear intention of meeting the needs of the labour market in this field of life sciences.

Who: Andalusian Initiative for Advanced Therapies

When: 2010-2015

13.2.

Promoting the **certification** of the training programme as an **ongoing training activity** through the Andalusian Agency for Healthcare Quality.

Who: Andalusian Initiative for Advanced Therapies

When: 2010-2015

13.3.

Promoting **alliances with the University sector to encourage its participation** in the training programme and proposing the consideration of university qualifications in order that an inter-university or even international programme can be configured.

Who: Andalusian Initiative for Advanced Therapies

When: 2010-2015

13.4.

Fostering a professional **training programme** in the manufacturing of specific Advanced Therapy products by accrediting Training Units both in Andalusia and beyond, through the Andalusian Agency for Healthcare Quality.

Who: Andalusian Initiative for Advanced Therapies

When: 2012-2015

Line 14. **Facilitating the training of researchers in the field of Advanced Therapies:**

14.1.

Promoting the **short-term mobility of research staff**, both basic and clinical, to research centres of excellence in Advanced Therapies in order to learn specific techniques in that field.

Who: Regional Ministry of Health

When: 2010-2015

14.2.

Increasing **collaboration agreements with cutting edge biotechnology companies, hospitals and research centres** in Advanced Therapies so that researchers from the region of Andalusia can undergo periods of advanced training there in this field of biomedicine.

Who: Fundación Progreso y Salud in collaboration with the Andalusian Initiative for Advanced Therapies

When: 2010-2015

14.3.

Favouring the **long-term mobility of post-doctoral researchers** to international centres of prestige in Advanced Therapies. These subsidies will be tied to the researcher's commitment to returning to one of the research groups from the thematic research centres (CABIMER, GENYO, and BIONAND) or health research institutes.

Who: Regional Ministry of Health and Regional Ministry of Economy, Innovation and Science

When: 2010-2015

14.4.

Promoting the **incorporation of international researchers for short periods of time** into research groups and into the lines prioritized in the programme by exploiting the national and international funding instruments that are currently underused in the scope of action of the Andalusian Public Health System.

Who: Research groups

When: 2010-2015

Servicio Andaluz de Salud. Consejería de Salud. Junta de Andalucía.

14.5.

Establishing a **programme of subsidies to co-finance training activities** for research staff in institutions of recognized international prestige in the areas prioritized in the Programme. This tool will serve to partially fund attendance at workshops, whenever the applicant has been awarded a subsidy by the organizing institution. The "raison d'être" for these subsidies is to prevent researchers from failing to attend advanced training activities for which they have already been awarded a subsidy on a competition basis.

Who: Regional Ministry of Health and Regional Ministry of Economy, Innovation and Science

When: 2010-2015

14.6.

Implementing **introductory training activities** in research in Advanced Therapies for pre- and postgraduate students.

Who: Fundación Progreso y Salud in collaboration with the Andalusian Initiative for Advanced Therapies

When: 2010-2015

Line 15. **Promoting the training of researchers in laboratory and people management**

15.1.

Providing researchers with **laboratory management tools** through specific training in project management and budget management tools aimed at laboratory managers and principal investigators.

Who: Local foundations in coordination with Fundación Progreso y Salud and in collaboration with the Andalusian Initiative for Advanced Therapies

When: 2nd half of 2010-2015

15.2.

Providing researchers with **people management tools**, through specific training in leadership, teamwork, incentive schemes and motivation, team training monitoring, etc. aimed at laboratory managers and principal investigators.

Who: Local foundations in coordination with Fundación Progreso y Salud and in collaboration with the Andalusian Initiative for Advanced Therapies

When: 2nd half of 2010-2015

5. COMMUNICATION ACTIONS UNDERTAKEN BY THE ANDALUSIAN INITIATIVE FOR ADVANCED THERAPIES

Strategic Objectives:

- Promoting the dissemination of knowledge in Advanced Therapies to society and establishing participation mechanisms.
- Fostering knowledge about the work of the Andalusian Initiative for Advanced Therapies.
- Cooperating with the Media, so that the information made available is more objective, truthful and as intelligible as possible.

Strategic lines and actions

Line 16. **Disseminating knowledge about the Initiative in areas of healthcare and academia**

16.1. ————

Carrying out an **information campaign aimed at university and healthcare professionals** in order for them to learn about the Initiative and what it is promoting in the field of Advanced Therapies. This campaign will be carried out by the Initiative in collaboration with the representatives from both the National Health System and the University, members of the Initiative's Governing Committee. This campaign will be aimed at Hospitals active in the Initiative's areas of interest and at the University Faculties which are closely linked to the field of biomedicine .

Who: Andalusian Initiative for Advanced Therapies in collaboration with Fundación Progreso y Salud and the Andalusian Universities

When: 2nd half of 2010-2015

Line 17. **Communicating scientifc advances in the area of Advanced Therapies to the general public, distinguishing between new discoveries and possible therapeutic applications, keeping the patient's perspective in mind.**

17.1. ————

Planning **lectures**. A "Cycle of lectures in Advanced Therapies" will be organized annually, aimed at the general public, university students and secondary school pupils.

Who: Andalusian Initiative for Advanced Therapies in collaboration with Fundación Progreso y Salud

When: 2nd half of 2010-2015

17.2. ————

Promoting a **collaboration agreement with RTVA (Andalusian Radio and Television)** and other media both to make and disseminate documentaries on Advanced Therapies. The making of educational reports, both on the radio and television, will be proposed. Televised information on these therapies will be featured in programmes such as "Salud al día" or "Tecnópolis", as well as in the News programmes. On the radio, collaboration channels will be sought in News programmes and a specific programme will be proposed for Radio Andalucía Información.

Who: Andalusian Initiative for Advanced Therapies in collaboration with Fundación Progreso y Salud, Patient Associations and RTVA

When: 2nd half of 2010-2015

17.3. ————

Publishing **think pieces and reports** in the regional printed media. These articles will be written to inform readers. The head of this area of the newspapers will be contacted and a publication schedule prepared.

Who: Andalusian Initiative for Advanced Therapies in collaboration with Fundación Progreso y Salud

When: 2nd half of 2010-2015

Line 18. **Favouring collaboration with scientific journalism.**

18.1. ————

Establishing smooth, truthful and effective communication between scientists and the general population. In addition to the dissemination initiatives promoted by the Regional Ministry of Health and the Regional Ministry of Economy, Innovation and Science as "Espacios Salud Investiga" or "Andalucía Investiga", the work of scientific journalism is also necessary. The Initiative will organize **scientific seminars for journalists**, where they will be told, in a simple and easily-understood manner, about advances in Advanced Therapies and where the research is heading. These seminars will complement the ongoing dialogue with journalists who require information from the Press Office of the Regional Ministry of Health or the Communication Division of Fundación Progreso y Salud.

Who: Andalusian Initiative for Advanced Therapies in collaboration with Fundación Progreso y Salud

When: 2011-2015

18.2. ————

Promoting the incorporation of teaching on scientific progress and clinical applications in the field of the Advanced Therapies within **university journalism studies**.

Who: Regional Ministry of Economy, Innovation and Science in collaboration with the Andalusian Universities and the Andalusian Initiative for Advanced Therapies

When: 2011-2015

Line 19 **Establishing mechanisms to communicate with patients and to enable their participation in the activities to be carried out by the Andalusian Initiative for Advanced Therapies.**

19.1. ————

Incorporating representatives from **patient associations** in the Governing Committee of the Andalusian Initiative for Advanced Therapies.

Who: Andalusian Initiative for Advanced Therapies

When: 2010-2015

19.2. ————

Facilitating communication with patients by creating an internet **forum** linked to the different citizen participation platforms set up by the Regional Ministry of Health.

Who: Andalusian Initiative for Advanced Therapies

When: 2010-2015

19.3.

Guaranteeing the appropriate information that must be given to those patients who take part in the **clinical trials** promoted by the Andalusian Initiative for Advanced Therapies. This guarantee will be safeguarded by the design of a **process to provide on-going, updated patient information** which clinics must supply during the trial and which also includes informed consent forms. In addition to complying with Spanish legislation and the guidelines of the Regional Ministry of Health, these forms will provide for the more specific aspects of these therapies.

Who: Andalusian Initiative for Advanced Therapies

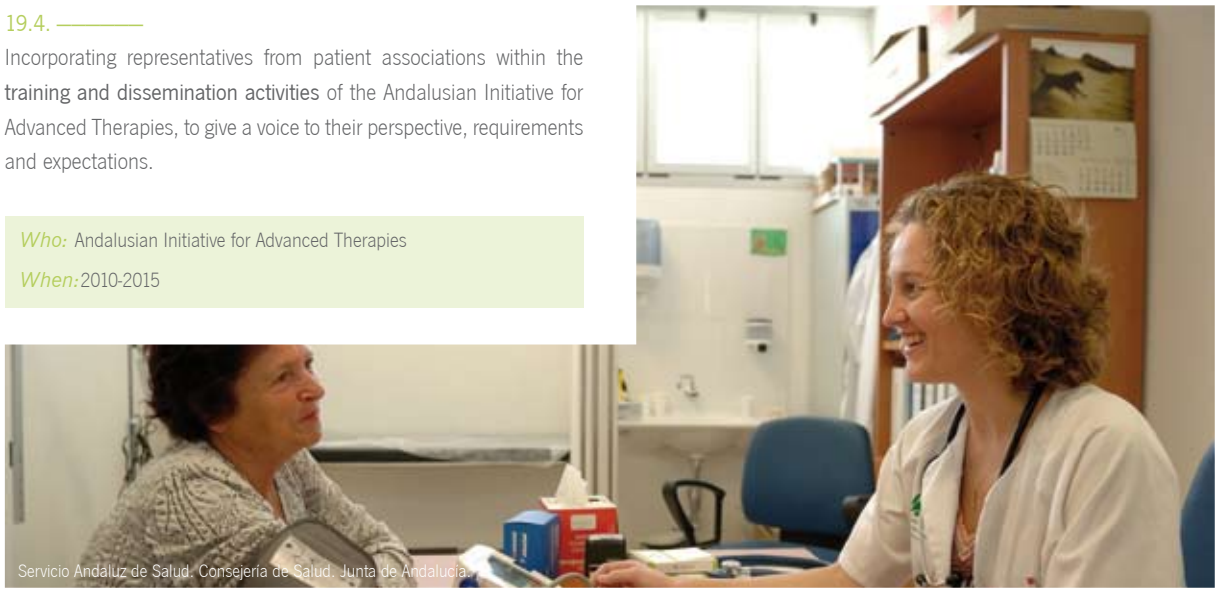
When: 2010-2015

19.4.

Incorporating representatives from patient associations within the **training and dissemination activities** of the Andalusian Initiative for Advanced Therapies, to give a voice to their perspective, requirements and expectations.

Who: Andalusian Initiative for Advanced Therapies

When: 2010-2015



Servicio Andaluz de Salud. Consejería de Salud. Junta de Andalucía.

8

EVALUATION OF THE ACTION PLAN

The success of this Action Plan must be evaluated in accordance with the number of safe and effective Advanced Therapies that finally become **accessible to citizens**

Servicio Andaluz de Salud. Consejería de Salud. Junta de Andalucía.

The mission of the Andalusian Initiative for Advanced Therapies is to promote the development of new therapies in order to improve the population's health and to incorporate innovative Advanced Therapies in the healthcare and progress of our region. Therefore, the success of this Action Plan must be evaluated in accordance with the number of safe and effective Advanced Therapies that finally become accessible to citizens.

As has been indicated in the justification of this Strategy and Action Plan, the course which must be followed for these new treatments to be accessible to the general population has not yet been clearly defined. This is due to the fact that Advanced Therapies comprise a whole range of very different possibilities, both from the standpoint of the processing required and that of the potential risks for their use in humans. In the case of therapies that require considerable manipulation and a high technological level for their development and manufacturing, it will be necessary to design effective knowledge transfer mechanisms that guarantee possible industrial use and which would ultimately favour the distribution of these products and their accessibility to the general population. Nevertheless, in the case of therapies very similar to others that have already been part of healthcare practice for some years, such as the transplant of hematopoietic progenitor cells, and where there is no manufacturing process as such, the health system, in collaboration with Regulatory Bodies, must set up flexible and speedy mechanisms to enable their incorporation into healthcare practice with the relevant quality and safety guarantees.

However, since Advanced Therapies began to be considered as drugs in 2003, the time when certain Advanced Therapies were already under development within the regulatory framework of cell and tissue transplants, some therapies at present have already been incorporated into the National Health System (SNS) Services Portfolio. These therapies have not followed the usual development of medicinal products with the performance of clinical trials in phases I, II and III, but they are still considered consolidated therapies.

The evaluation of this Action Plan must, therefore, be based on three basic elements:

1. Incorporation of those **medicinal products included in the National Health System Services Portfolio** into the healthcare practice of the Andalusian Public Health System.

2. Incorporation into the healthcare practice of the Andalusian Public Health System of those **medicinal products**, not yet included in the National Health System Services Portfolio, which are being developed in Andalusia and which do not entail a manufacturing process as such, which means their **commercial development is not possible**.

3. Transfer of knowledge in the case of therapies that require considerable manipulation and a high technological level for their development and manufacturing, which will guarantee their possible **industrial use and incorporation in the market**.

On the other hand, we must not forget that the economic cycle for the development of new therapies and for their access to the market clearly exceeds the 6 year period this Action Plan is limited to. Therefore, the evaluation must be based on indicators that make it possible to know the evolution of knowledge generation and translation to clinical practice and results transfer.

The indicators will be periodically evaluated by the Andalusian Initiative for Advanced Therapies in their biennial report on the development of the Action Plan. This report will be sent to the External Advisory Committee of the Andalusian Initiative for Advanced Therapies which will meet to prepare their conclusions. The report, together with the conclusions of the Advisory Committee, will be sent to the Governing Committee, which will meet to assess the relevance of introducing modifications in the Action Plan.

Below, we give a reduced number of indicators, selected due to the feasibility of their measurement, which make it possible to know the evolution of knowledge generation and translation to clinical practice and results transfer.

Knowledge generation:

Indicator 1:

- Increase in the number of researchers working in Advanced Therapy research activities in Andalusia inside the Andalusian Public Health System.

- Sources of information: FPS inventory of research groups.

- Standard: a progressive increase should be observed over the 6 years of no less than 10% every two years.

Indicator 2:

- Number of PAIDI research groups working in the biotechnology field

- Sources of information: Regional Ministry of Economy, Innovation and Science inventory of PAIDI research Groups.

- Standard: the number in the first years must be increased, since the opening of new research centres for Advanced Therapies is planned. After the first 2 years of the introduction of these centres, at least 50% of the researchers planned for each centre must have been incorporated, 75% after 4 years and 90% after 6 years.

Clinical translation:

Indicator 3:

- Number of original articles in indexed journals published by researchers working in Advanced Therapy research activities in Andalusia within the Andalusian Public Health System or in research centres associated with the Regional Ministry of Health.
- Sources of information: FPS inventory of research groups and electronic databases (MEDLINE, EMBASE, etc.).
- Standard: the standard is not currently available. It will be implemented after the first analyses, but its progressive increase over the 6 years should be verified.

Indicator 4:

- Personal index h of the researchers working in Advanced Therapy research activities in Andalusia within the Andalusian Public Health System or in research centres associated with the Regional Ministry of Health.
- Sources of information: FPS inventory of research groups and Web of Knowledge (WOK).
- Standard: the progressive incorporation of new researchers, both young and senior does not make it possible to predict if the mean of the index h will increase or decrease. However, an increase in the number of researchers reaching index h levels over 15 should be observed.

Indicator 5:

- Number of Advanced Therapy products under research, authorized by the Spanish Agency of Medicines and Medicinal Products (AEMPS), produced in Andalusian Public Health System centres or associated with the Regional Ministry of Health.
- Sources of information: Andalusian Initiative for Advanced Therapies.
- Standard: a progressive increase should be observed over the 6 years, until the point is reached at which at least one product has been authorized for research in each Advanced Therapy AEMPS accredited GMP laboratory belonging to Andalusian Public Health System centres or associated with the Regional Ministry of Health.

Indicator 6:

- Number of clinical trials promoted by the Andalusian Initiative for Advanced Therapies authorized by the Spanish Agency of Medicines and Medicinal Products.
- Sources of information: Andalusian Initiative for Advanced Therapies.
- Standard: it is not possible to define a standard, but a progressive increase should be observed over the 6 years.

Indicator 7:

Total n° of authorized phase III clinical trials promoted by the Initiative x 100

Total n° of authorized clinical trials promoted by the Initiative

- Sources of information: Andalusian Initiative for Advanced Therapies.
- Standard: 10% by the end of the 6 years of this Action Plan.

Indicator 8:

N° of authorized clinical trials promoted by the Initiative x 100

Total n° of authorized clinical trials in Andalusia

- Sources of information: Andalusian Initiative for Advanced Therapies and Regional Committee for Clinical Trials.
- Standard: the standard is not currently available. It will be implemented after the first analyses, but its progressive increase over the 6 years should be verified.

Transfer and application of results:

Indicator 9:

- Increase with respect to the previous year in the number of patents annually registered in that field of Advanced Therapies owned, at least partially, by the Andalusian Public Health System.
- Sources of information: Office of Technology Transfer of the Andalusian Public Health System.
- Standard: a progressive increase should be observed over the 6 years, not less than 20% every two years.

Indicator 10:

N° of licensed patents registered since 2010 in the field of Advanced Therapies owned, at least partially, by the Andalusian Public Health System x 100

N° of patents registered since 2010 in the field of Advanced Therapies owned, at least partially, by the Andalusian Public Health System

- Sources of information: Office of Technology Transfer of the Andalusian Public Health System.
- Standard: the standard is not currently available. It will be implemented after the first analyses, but its progressive increase over the 6 years should be verified.

Indicator 11:

N° of licensed patents registered since 2010,yielding royalties, in the field of Advanced Therapies owned, at least partially, by the Andalusian Public Health System x 100

N° of patents licensed since 2010, in the field of Advanced Therapies owned, at least partially, by the Andalusian Public Health System

- Sources of information: Office of Technology Transfer of the Andalusian Public Health System.
- Standard: the standard is not currently available. It will be implemented after the first analyses, but its progressive increase over the 6 years should be verified.

Indicator 12:

- N° of active *start-up* companies in the field of Advanced Therapies promoted by the OTT of the Andalusian Public Health System – Andalusian Initiative for Advanced Therapies after 2010.
- Sources of information: Office of Technology Transfer of the Andalusian Public Health System.
- Standard: a progressive increase should be observed over the 6 years.

Indicator 13:

- Annual increase in the number of collaborations between research groups linked with the Regional Ministry of Health and private entities in the field of Advanced Therapies.
- Sources of information: Office of Technology Transfer of the Andalusian Public Health System.
- Standard: an increase of no less than 20% should be observed every two years.

Indicator 14:

N° of consolidated therapies incorporated in the Andalusian Public Health System x 100

N° of consolidated therapies incorporated in the National Health System Services Portfolio

- Sources of information: Andalusian Health System and National Health System Services Portfolio.
- Standard: 100%

9

GOVERNING, ADVISORY AND TECHNICAL COMMITTEES

This Action Plan has been prepared by **7 working groups**

This Action Plan has been prepared by 7 **working groups** (whose composition is set out at the start of this document), the **Advisory Committee** which supervised its execution and the **Governing Committee** which defined its Mission, Vision, Strategic Principles and Objectives and which was further responsible for the final approval of this Plan. The composition of the Committees mentioned here is listed in chapter V relating to the Working Methodology. Since the work connected with the drawing up of the Action Plan is now complete, new committees need to be formed in accordance with its implementation. More information concerning these committees is set out below:

Governing Committee of the Andalusian Initiative for Advanced Therapies

Composition:

1.
The Secretary General of Quality and Modernization of the Regional Ministry of Health

2.
The Secretary General of Universities, Research and Technology of the Regional Ministry of Economy, Innovation and Science

3.
The Director-General for Knowledge Management, Quality and Research of the Regional Ministry of Health

4.
The Director-General for Research, Technology and Enterprise of the Regional Ministry of Economy, Innovation and Science

5.
The Director-General of the Andalusian Health Service

6.
The Director of the Andalusian Innovation and Development Agency

7.
The Executive Director of the Andalusian Initiative for Advanced Therapies

8.
The General Manager of Fundación Progreso y Salud

9. / 10.
Two rotating Vice-Chancellors for research across Andalusian universities

11. / 13.
The Directors of the Cell Therapy and Regenerative Medicine, Clinical Genetics and Genomic Medicine and Nanomedicine Programmes.

14.
The Director of the Strategic Plan for Research, Development and Innovation in Health

15.
A representative of the Spanish Association of Bioenterprises (Asociación Española de Bioempresas) (ASEBIO)

16.
A representative from the pharmaceutical industry

17. / 18.
Two representations from Patient Associations

Duties:

1. Selecting the members of the External Advisory Committee of the Andalusian Initiative for Advanced Therapies as proposed by the Directors or Coordinators of the Cell Therapy and Regenerative Medicine, Clinical Genetics and Genomic Medicine and Nanomedicine programmes, and the Management of the Initiative.
2. Assessing the relevance of introducing modifications to the Action Plan, on the basis of the two-yearly evaluations to be carried out.

External Advisory Committee of the Andalusian Initiative for Advanced Therapies

Composition:

This Committee will be composed of a multidisciplinary panel of Spanish and international experts, incorporating leading basic and clinical researchers in these areas of research, experts in results transfer, venture capital and capital from the business sectors.

Duties:

1. It will participate in the prioritization of the strategies of the Andalusian Initiative for Advanced Therapies. The selection of the lines to prioritise will result from carrying out a scientific-technical evaluation which will also assist in their classification into short-term lines (specific lines that are already in clinical research or close to it) and medium/long-term lines, incorporating into the classification the relevant information for their selection and temporary classification.

2. It will participate in the two-yearly evaluation of the Action Plan, giving its conclusions on the results of the evaluation report produced by the Management of the Andalusian Initiative for Advanced Therapies.

Technical Committee for Clinical Research

Composition:

Permanent members:

- A Technical Director from one of the Cell Therapy Units in the Region.
- Three physicians from the Andalusian Public Health System with experience in implementing and developing clinical trials and who represent one of the areas considered of maximum interest.
- A basic researcher in Advanced Therapies with knowledge and experience in their translational aspects.
- The Initiative's Medical and Regulatory Affairs Coordinator, who will act as coordinator of the Technical Committee.
- The Initiative's Head of Clinical trials.
- A representative from FPS.

Non-permanent members:

Depending on the matters tackled in the Technical Committee meetings, the following may be convened:

The directors of the research programmes in:

- Cell Therapy and Regenerative Medicine
- Clinical Genetics and Genomic Medicine
- Nanomedicine

Directors of healthcare plans. Without prejudicing others that may be considered later, the following could, in principle, be envisioned:

- Andalusian Comprehensive Oncology Plan
- Andalusian Comprehensive Diabetes Plan
- Andalusian Comprehensive Plan for the care of Heart Disease
- Andalusian Plan for Alzheimer's
- Andalusian Genetic Plan
- Care Plan for people affected with Rare Diseases
- Andalusian Plan for Palliative Care
- Comprehensive Care Plan in the Event of Accidents

Duties:

- Establishing and periodically reviewing the areas of maximum interest in the development of clinical trials. Given that the advances in basic and translational research in Cell Therapy, Gene therapy and Nanomedicine are happening very fast, it is considered essential to review, at least once a year, the areas of maximum interest for the Initiative for the carrying out of clinical trials.
- Proposing technical criteria that establish the rules for a centre to be accepted in the participation of a clinical trial, as well as the criteria so that a centre can also be withdrawn after its incorporation. It will also be in charge of assessing compliance with these criteria.
- Encouraging communication between the Initiative and the independent research groups through evaluating the relevance of their clinical trial proposals.
- Giving advice to the clinical research groups whose proposals have been considered relevant in all necessary technical or fund-seeking aspects.

- Proposing support measures and innovative ideas to the Andalusian Initiative for Advanced Therapies in their support of the independent clinical research groups whose proposals are considered pertinent.

- Fostering cooperation between clinical research groups. Based on the knowledge of all initiatives arising in the Region, the Technical Committee will favour the associations of different groups with similar research lines in order to generate Multicentric and Coordinated Trials. It will be considered a priority to join forces in this regard in order to promote efficient clinical trials with a high number of patients. In this sense, the role of the Technical Committee is fundamental as it will have first hand knowledge of all the groups' proposals and it can use this knowledge to foster the association of groups and cohesion of the trials.

It will be possible to cover most duties of the Technical Committee with the members proposed. However, if no members of this group have experience in the area/pathology proposed for research, advice can be requested from the Initiative's Advisory Committee, or other experts, if necessary.

How it will work:

- It will be constituted formally once a year to evaluate the priorities and/or strategies of clinical research in Advanced Therapies as well as other areas considered of maximum interest. After this meeting, a Technical Report will be prepared which will be sent to the Initiative's Management for its evaluation and decision making. Likewise, it will be sent to the New Advanced Therapies Trends Observatory, with whom collaboration will be maintained.

- Proposals received electronically will be permanently reviewed and evaluated in order to judge their relevance and advise the research groups in the aforementioned areas (possible associations with other groups, funding search, trial authorization, etc). These meetings may be held online.

- On a permanent basis, it will review the periodic monitoring reports of the clinical trials prepared by the Initiative, including the reports to be sent to the Clinical Research Ethics Committee, to enable it to assess the relevance of incorporating or withdrawing some centres. These meetings may be held online.

A Safety Commission will be established in this Committee to analyse any incidents that may affect patient safety and the serious and unexpected adverse events that may arise in the course of the clinical trials in Advanced Therapies promoted by the Andalusian Initiative for Advanced Therapies. This Commission will be permanently composed of:

- The Initiative's Medical and Regulatory Affairs Coordinator, who will act as Commission coordinator

- The Initiative's Head of Clinical Trials

- Representative of the Andalusian Pharmacovigilance Centre

- 1 Technical Director from one of the Cell Therapy Units which are already in place in the Region

- 1 specialist in internal medicine

This Commission will have the experts required depending on the safety aspects concerned.

ANNEXE 1

NON-COMMERCIAL CLINICAL TRIALS WITH STEM CELLS IN ANDALUSIA IN FEBRUARY 2010

Cardiology

DILATED MYOCARDIOPATHY.

Clinical trial titled "Effect of intracoronary infusion of bone marrow progenitor cells on myocardial regeneration in patients with dilated myocardiopathy. Clinical-biological study."

Principal investigator:

Dr Suárez de Lezo.
Hospital Universitario Reina Sofía, Cordoba.

ACUTE MYOCARDIAL INFARCTION.

Clinical trial titled "Myocardial regeneration after intracoronary implantation of autologous bone marrow stem cells in patients with acute myocardial infarctions with anterior localization."

Principal investigators:

Dr Suárez de Lezo.
Hospital Universitario Reina Sofía, Cordoba.

Dr Inmaculada Concepción Herrera Arroyo.
Hospital Universitario Reina Sofía, Cordoba.

Neurology

MULTIPLE SCLEROSIS.

Clinical trial titled "Multicentric, randomized, placebo-controlled, phase I/II clinical trial, to evaluate the safety and feasibility of therapy with two different doses of autologous mesenchymal stem cells from adipose tissue (CeTMAd) in patients with secondary progressive multiple sclerosis, who do not appropriately respond to registered treatments."

Principal investigators:

Dr Oscar Fernández Fernández.
Hospital Universitario Carlos Haya, Malaga.

Dr Guillermo Izquierdo Ayudo.
Hospital Universitario Virgen Macarena, Seville.

STROKE.

Clinical trial titled "Reader-blinded open study of the efficacy of autologous bone marrow mononuclear cells in cell regeneration in patients with acute ischemic stroke of the Middle Cerebral Artery."

Principal investigators:

Dr Jesús Otero.
Hospital Universitario Central de Asturias.

Dr Alberto Gil Peralta.
Hospital Universitario Virgen del Rocío, Seville.

Immunology

GRAFT VERSUS HOST DISEASE.

Clinical trial titled "Multricentric, randomized, controlled, phase I/II clinical trial, to evaluate the safety and feasibility of therapy with two different doses of autologous mesenchymal stem cells from adipose tissue in patients with extensive chronic Graft versus Host disease."

Principal investigators:

Dr Manuel Jurado Chacón.
Hospital Universitario Virgen de las Nieves, Granada.

Dr Álvaro Urbano Ispizúa.
Hospital Universitario Virgen del Rocío, Seville.

Dr Carlos Solano Vercet.
Hospital Universitario Clínico, Valencia.

Dr Sebastián Garzón López.
Hospital Universitario de Jerez de la Frontera, Cadiz.

Peripheral vascular

CRITICAL LIMB ISCHEMIA IN DIABETIC PATIENTS.

1). Clinical trial titled "Application of cell regeneration therapy in chronic critical limb ischemia syndrome in diabetic patients."

Principal investigators:

Dr Rafael Ruiz Salmerón.
Hospital Universitario Virgen Macarena, Seville.

Dr Antonio de la Cuesta.
Hospital San Lázaro, Seville.

2). Clinical trial titled "Phase II clinical trial on therapeutic angiogenesis with autologous bone marrow mononuclear cells in diabetic patients with non-revascularizable chronic critical limb ischemia."

Principal investigators:

Dr Inmaculada Concepción Herrera Arroyo.
Hospital Universitario Reina Sofía, Cordoba.

Dr Francisco Tadeo Gómez Ruiz.
Hospital Universitario Virgen del Rocío, Seville.

Dr Diego de Alcalá Martínez Gómez.
Hospital Universitario Morales Meseguer, Murcia.

Dr José Patricio Linares Palomino.
Hospital Universitario San Cecilio, Granada.

Dr Vicente García Róspide.
Hospital Universitario Virgen de las Nieves, Granada.

3). Clinical trial titled "Use of mesenchymal stem cells from adipose tissue (CeTMAd) as cell regeneration therapy in chronic critical limb ischemia syndrome in diabetic patients."

Principal investigators:

Dr Rafael Ruiz Salmerón.
Hospital Universitario Virgen Macarena, Seville.

Dr Antonio de la Cuesta.
Hospital San Lázaro, Seville.

CRITICAL LIMB ISCHEMIA IN NON-DIABETIC PATIENTS.

1). Clinical trial titled "Phase II clinical trial on therapeutic angiogenesis with autologous bone marrow mononuclear cells in non-diabetic patients with non-revascularizable chronic critical limb ischemia."

Principal investigators:

Dr Inmaculada Concepción Herrera Arroyo.
Hospital Universitario Reina Sofía, Cordoba.

Dr Francisco Tadeo Gómez Ruiz.
Hospital Universitario Virgen del Rocío, Seville.

Dr Diego de Alcalá Martínez Gómez.
Hospital Universitario Morales Meseguer, Murcia.

Dr José Patricio Linares Palomino.
Hospital Universitario San Cecilio, Granada.

Dr Vicente García Róspide.
Hospital Universitario Virgen de las Nieves, Granada.

2). Clinical trial titled "Open, randomized, multicentric phase I/II clinical trial for the study of the use of mesenchymal stem cells from adipose tissue (CeTMAd) as cell regeneration therapy in chronic critical limb ischemia syndrome in non-diabetic patients."

Principal investigators:

Dr Rafael Ruiz Salmerón.
Hospital Universitario Virgen Macarena, Seville.

Dr Antonio de la Cuesta.
Hospital San Lázaro, Seville.

Digestive

HEPATIC REGENERATION.

Clinical trial titled "Open, randomized, multicentric phase II clinical trial on the therapeutic use of the intraportal infusion of autologous bone marrow mononuclear cells as potentiator of hepatic regeneration before performing extended hepatic resections."

Principal investigators:

Dr Javier Padillo Ruiz.
Hospital Universitario Virgen del Rocío, Seville.

Dr Antonio Galindo Galindo.
Hospital Universitario Nuestra Señora de Valme, Seville.

ANNEXE 2

NETWORK OF HEALTH RESEARCH MANAGEMENT FOUNDATIONS IN ANDALUSIA

Autonomous area

FUNDACIÓN PROGRESO Y SALUD

Address
Avda. Américo Vespucio 5, Bloque 2, 2°Planta Izq.
Parque Científico y Tecnológico Cartuja 93 (41092 Sevilla)

Telephone: 955 040 450

Mail / Web:
fundacion.progreso.salud@juntadeandalucia.es
www.juntadeandalucia.es/fundacionprogresoysalud

Provincial and interprovincial area

FABIS. FUNDACIÓN ANDALUZA BETURIA PARA LA INVESTIGACIÓN EN SALUD

Address:
Hospital Juan Ramón Jiménez, 4ª Planta
Ronda Norte, s/n (21005 Huelva)

Telephone: 959 016 805 / 959 016 760

Mail / Web:
secretaria@fabis.org
www.fabis.org

FCÁDIZ. FUNDACIÓN PARA LA GESTIÓN DE LA INVESTIGACIÓN BIOMÉDICA DE CÁDIZ

Address:
Hospital Universitario Puerta del Mar,
Avda. Ana de Viya, 21 9ª Pl. (11009 Cádiz)

Telephone: 956 245 019

Mail:
fundacion.cadiz@juntadeandalucia.es

FIBICO. FUNDACIÓN PARA LA INVESTIGACIÓN BIOMÉDICA DE CÓRDOBA

Address:
Avda. Menéndez Pidal, s/n. Edif. Consultas Externas (14004 Córdoba)

Telephone: 957 012 911 / 957 012 914 / 957 736 483

Mail:
fibicor@gmail.com

IMABIS. FUNDACIÓN INSTITUTO MEDITERRÁNEO PARA EL AVANCE DE LA BIOTECNOLOGÍA Y LA INVESTIGACIÓN SANITARIA (MÁLAGA)

Address:
Hospital Carlos Haya. Avda. Carlos Haya, nº 25. Local bajo (29010 Málaga)

Telephone: 951 440 260

Mail / Web:
secretaria@fundacionimabis.org
www.imabis.org

FISEVI. FUNDACIÓN PÚBLICA ANDALUZA PARA LA GESTIÓN DE LA INVESTIGACIÓN EN SALUD DE SEVILLA

Address:
Hospital Universitario Virgen del Rocio. Edif. Laboratorio, 6ª Pl.
Avda. Manuel Siurot, s/n (41013 Sevilla)

Telephone: 955 013 284

FIBAO. FUNDACIÓN PÚBLICA ANDALUZA PARA LA INVESTIGACIÓN BIOSANITARIA EN ANDALUCÍA ORIENTAL "ALEJANDRO OTERO" (ALMERÍA, GRANADA, JAÉN)

Address:
c/ Dr. Azpitarte, nº4 - 4º (18012 Granada)

Telephone: 958 020 245

Web:
www.fibao.es

ANNEXE 3

RESEARCHERS IN ANDALUSIA WORKING IN THE FIELD OF ADVANCED THERAPIES

Identified through the databases of the Regional Ministry of Health's calls for subsidies

Francisco Javier Gallego Rojo
Empresa Pública Hospitalaria Poniente de Almería.
ALMERÍA

José Antonio López Escámez
Empresa Pública Hospitalaria Poniente de Almería.
ALMERÍA

Mª Ángeles Vázquez
Hospital Torrecárdenas
ALMERÍA

Antonio José Fernández Barbero
Universidad de Almería
ALMERÍA

José Luis Guzmán
Hospital Universitario de Jerez
CÁDIZ

Alfonso María Lechuga Sancho
Hospital Universitario Puerta del Mar
CÁDIZ

Antonio Campos Caro
Hospital Universitario Puerta del Mar
CÁDIZ

Antonio Nieto Díaz
Hospital Universitario Puerta del Mar
CÁDIZ

Francisco Mora López
Hospital Universitario Puerta del Mar
CÁDIZ

Irene Cózar Castellano
Hospital Universitario Puerta del Mar
CÁDIZ

José Antonio Girón González
Hospital Universitario Puerta del Mar
CÁDIZ

Juan Muñoz
Hospital Universitario Puerta del Mar
CÁDIZ

María del Carmen Segundo Iglesias
Hospital Universitario Puerta del Mar
CÁDIZ

Rafael Sierra Camerino
Hospital Universitario Puerta del Mar
CÁDIZ

Francisco J. García
Hospital Universitario Puerto Real
CÁDIZ

Amalia Palacios Eito
Hospital Universitario Reina Sofía
CÓRDOBA

Francisco Javier Delgado Lista
Hospital Universitario Reina Sofía
CÓRDOBA

Inmaculada Herrera Arroyo
Hospital Universitario Reina Sofía
CÓRDOBA

Jordí Muntané Relat
Hospital Universitario Reina Sofía
CÓRDOBA

Juan Alberto Ruano Ruiz
Hospital Universitario Reina Sofía
CÓRDOBA

Manuel de la Mata García
Hospital Universitario Reina Sofía
CÓRDOBA

Pablo Pérez Martinez
Hospital Universitario Reina Sofía
CÓRDOBA

Pedro Aljama García
Hospital Universitario Reina Sofía
CÓRDOBA

Eduardo Collantes
Hospital Universitario Reina Sofía
CÓRDOBA

Enrique Cantillo Baños
Hospital Universitario Reina Sofía
CÓRDOBA

Ignacio López Villalba
Hospital Universitario Reina Sofía
CÓRDOBA

Joaquín Sánchez García
Hospital Universitario Reina Sofía
CÓRDOBA

Josefa Requena Tapias
Hospital Universitario Reina Sofía
CÓRDOBA

Juan Mariano Rodríguez Portillo
Hospital Universitario Reina Sofía
CÓRDOBA

María Sagrario Cañadillas López
Hospital Universitario Reina Sofía
CÓRDOBA

Pedro Gómez
Hospital Universitario Reina Sofía
CÓRDOBA

Ramón Cañete Estrada
Hospital Universitario Reina Sofía
CÓRDOBA

José Román Gómez
IMIBIC
CÓRDOBA

Manuel Ruiz Rubio
IMIBIC
CÓRDOBA

Francisco Gracia-Navarro
Universidad de Córdoba
CÓRDOBA

Isaac Túnez Fiñana
Universidad de Córdoba
CÓRDOBA

José Manuel Quesada Gómez
Universidad de Córdoba
CÓRDOBA

Miguel Valcárcel
Universidad de Córdoba
CÓRDOBA

Alicia Barroso del Jesús
Banco Andaluz de Células Madre
GRANADA

Cristina Palma Carazo
Banco Andaluz de Células Madre
GRANADA

Francisco Martín Molina
Banco Andaluz de Células Madre
GRANADA

José Luis García Pérez
Banco Andaluz de Células Madre
GRANADA

Manuel Masip Ordóñez
Banco Andaluz de Células Madre
GRANADA

Pablo Menéndez Buján
Banco Andaluz de Células Madre
GRANADA

Paola Elizabeth Leone Campo
Banco Andaluz de Células Madre
GRANADA

Inmaculada Concepción
Delgado Calvo-Flores
Centro Regional Transfusiones Sanguíneas
Granada
GRANADA

José Antonio Lorente Acosta
GENYO
GRANADA

Juan Carlos
Rodríguez-Manzaneque Escribano
GENYO
GRANADA

Mª José Serrano Fernández
GENYO
GRANADA

Marta Eugenia Alarcón Riquelme
GENYO
GRANADA

Benito Mirón Pozo
Hospital Universitario San Cecilio
GRANADA

Enrique García Olivares
Hospital Universitario San Cecilio
GRANADA

José Fernando Florido López
Hospital Universitario San Cecilio
GRANADA

José Mariano Ruiz
de Almodóvar Rivera
Hospital Universitario San Cecilio
GRANADA

José Patricio Linares Palomino
Hospital Universitario San Cecilio
GRANADA

Mª Esther Fárez Vidal
Hospital Universitario San Cecilio
GRANADA

Manuel Miguel Guerrero Fernández
Hospital Universitario San Cecilio
GRANADA

Miguel Alaminos Mingorance
Hospital Universitario San Cecilio
GRANADA

Norberto Ortego Centeno
Hospital Universitario San Cecilio
GRANADA

Paloma Muñoz de Rueda
Hospital Universitario San Cecilio
GRANADA

Ana Linares Gil
Hospital Universitario Virgen de las Nieves
GRANADA

Antonio Irigoyen Medina
Hospital Universitario Virgen de las Nieves
GRANADA

Antonio Rodríguez Fernández
Hospital Universitario Virgen de las Nieves
GRANADA

Daniel Garrote Lara
Hospital Universitario Virgen de las Nieves
GRANADA

Federico Garrido Torres-Puchol
Hospital Universitario Virgen de las Nieves
GRANADA

Francisco Ruiz-Cabello Osuna
Hospital Universitario Virgen de las Nieves
GRANADA

José Antonio Ferrón Orihuela
Hospital Universitario Virgen de las Nieves
GRANADA

Juan Salvatierra Osorio
Hospital Universitario Virgen de las Nieves
GRANADA

Mª Dolores Collado Escobar
Hospital Universitario Virgen de las Nieves
GRANADA

Manuel de la Rosa Fraile
Hospital Universitario Virgen de las Nieves
GRANADA

Manuel Jurado Chacón
Hospital Universitario Virgen de las Nieves
GRANADA

Margarita Aguilera Gómez
Hospital Universitario Virgen de las Nieves
GRANADA

Miguel Ángel López Nevot
Hospital Universitario Virgen de las Nieves
GRANADA

Natalia Aptsiauri Aptsiauri
Hospital Universitario Virgen de las Nieves
GRANADA

Pilar López Garrido
Hospital Universitario Virgen de las Nieves
GRANADA

Pilar Navarro
Hospital Universitario Virgen de las Nieves
GRANADA

Rafael Ríos Tamayo
Hospital Universitario Virgen de las Nieves
GRANADA

Ricardo Fernández Valadés
Hospital Universitario Virgen de las Nieves
GRANADA

Sebastián Manzanares Galán
Hospital Universitario Virgen de las Nieves
GRANADA

Antonia Aránega Jiménez
Universidad de Granada
GRANADA

Armando Blanco Morón
Universidad de Granada
GRANADA

Concepción Ruiz Rodríguez
Universidad de Granada
GRANADA

Delfi Bastos González
Universidad de Granada
GRANADA

Enrique Álvarez Manzaneda Roldán
Universidad de Granada
GRANADA

José Carlos Prados Salazar
Universidad de Granada
GRANADA

Juan Antonio Marchal Corrales
Universidad de Granada
GRANADA

Juan Niclós Gutiérrez
Universidad de Granada
GRANADA

Mª José Alejandre Pérez
Universidad de Granada
GRANADA

Vicente Crespo
Universidad de Granada
GRANADA

César Ramírez Tortosa
Hospital Complejo Hospitalario de Jaén
JAÉN

Maite Ferrín Erdozain
Hospital Complejo Hospitalario de Jaén
JAÉN

Manuela Gassó Campos
Hospital Complejo Hospitalario de Jaén
JAÉN

Miguel Ruiz Veguilla
Hospital Complejo Hospitalario de Jaén
JAÉN

Irene Peláez
Hospital Materno Infantil
JAÉN

Antonio José Caruz Arcos
Universidad Jaén
JAÉN

María del Monte Trujillo Pérez
Centro de atención especializada Jaén
JAÉN

Elena Baixeras Llanos
Banco de Sangre de Cordón Umbilical de Andalucía
MÁLAGA

Enrique Guerado Parra
Empresa Pública Hospitalaria Costa del Sol
MÁLAGA

Alejandro Hugo Unda Freire
Hospital Regional Universitario Carlos Haya
MÁLAGA

Antonio Alonso Ortiz
Hospital Regional Universitario Carlos Haya
MÁLAGA

Antonio Fernández Nebro
Hospital Regional Universitario Carlos Haya
MÁLAGA

Antonio L. Cuesta Muñoz
Hospital Regional Universitario Carlos Haya
MÁLAGA

Federico J. Casimiro-Soriguer Escofet
Hospital Regional Universitario Carlos Haya
MÁLAGA

Guillermo Estivill Torrus
Hospital Regional Universitario Carlos Haya
MÁLAGA

Laura Leyva Fernández
Hospital Regional Universitario Carlos Haya
MÁLAGA

Manuel Cobo Dols
Hospital Regional Universitario Carlos Haya
MÁLAGA

Mª José Bravo Romero
Hospital Regional Universitario Carlos Haya
MÁLAGA

Manuel Macías González
Hospital Regional Universitario Carlos Haya
MÁLAGA

Miguel Ángel Lucena Robles
Hospital Regional Universitario Carlos Haya
MÁLAGA

Miguel Blanca Gómez
Hospital Regional Universitario Carlos Haya
MÁLAGA

Oscar Fernández Fernández
Hospital Regional Universitario Carlos Haya
MÁLAGA

Pedro Ruiz
Hospital Regional Universitario Carlos Haya
MÁLAGA

Yolanda de Diego Otero
Hospital Regional Universitario Carlos Haya
MÁLAGA

Cristóbal Marchal Escalona
Hospital Universitario Virgen de la Victoria
MÁLAGA

Eduardo de Teresa Galván
Hospital Universitario Virgen de la Victoria
MÁLAGA

Emilio Alba Conejo
Hospital Universitario Virgen de la Victoria
MÁLAGA

F.J. Tinahones Madueño
Hospital Universitario Virgen de la Victoria
MÁLAGA

José Manuel Trigo Pérez
Hospital Universitario Virgen de la Victoria
MÁLAGA

José Miguel Jurado García
Hospital Universitario Virgen de la Victoria
MÁLAGA

Mª Isabel Sáez
Hospital Universitario Virgen de la Victoria
MÁLAGA

Miguel Martín Hernández
Hospital Universitario Virgen de la Victoria
MÁLAGA

Pedro Valdivielso Felices
Hospital Universitario Virgen de la Victoria
MÁLAGA

Ana Isabel Heiniger Mazo
IMABIS
MÁLAGA

Fermín Mayoral Cleries
IMABIS
MÁLAGA

Javier Márquez
IMABIS
MÁLAGA

Jesús Santos
IMABIS
MÁLAGA

Juan Ángel Bellón Saameño
IMABIS
MÁLAGA

Juan de Dios Colmenero
IMABIS
MÁLAGA

Mª Dolores Bautista Ojeda
IMABIS
MÁLAGA

Mª Isabel Lucena
IMABIS
MÁLAGA

Manuel Benavides Orgaz
IMABIS
MÁLAGA

Pilar Morata Losa
IMABIS
SEVILLA

Raúl Andrade Bellido
IMABIS
MÁLAGA

Santiago del Castillo Álvarez
IMABIS
SEVILLA

Ezequiel Pérez-Inestrosa Villatoro
Universidad de Málaga
MÁLAGA

Francisca Sánchez Jiménez
Universidad de Málaga
MÁLAGA

José Becerra Ratia
Universidad de Málaga
MÁLAGA

José María Pérez Pomares
Universidad de Málaga
MÁLAGA

Juan Francisco Arenas Rosado
Universidad de Málaga
MÁLAGA

Leonor Santos Ruiz
Universidad de Málaga
MÁLAGA

Ramón Muñoz-Chapuli Oriol
Universidad de Málaga
MÁLAGA

Abdelkrim Hmadcha Afif
CABIMER
SEVILLA

Abelardo López Rivas
CABIMER
SEVILLA

Alfredo Rodríguez Tebar
CABIMER
SEVILLA

Ana Isabel Rojas González
CABIMER
SEVILLA

Bernat Soria
CABIMER
SEVILLA

Félix Prado Velasco
CABIMER
SEVILLA

Francisco Martín Bermudo
CABIMER
SEVILLA

Francisco Bedoya
CABIMER
SEVILLA

Jaime Muñoz Franco
CABIMER
SEVILLA

José Antonio Pintor Toro
CABIMER
SEVILLA

José Antonio Sánchez Alcázar
CABIMER
SEVILLA

José Reyes
CABIMER
SEVILLA

Manuel Álvarez Dolado
CABIMER
SEVILLA

Plácido Navas Lloret
CABIMER
SEVILLA

Rosa María Ríos
CABIMER
SEVILLA

Shomi Bhattacharya
CABIMER
SEVILLA

Asunción Fernández Camacho
Centro de Materiales de Sevilla
SEVILLA

Antonio Espino Montoro
Hospital de la Merced de Osuna
SEVILLA

Alberto Gil Peralta
Hospital Universitario Virgen del Rocío
SEVILLA

Álvaro Urbano Ispizúa
Hospital Universitario Virgen del Rocío
SEVILLA

Antonio Núñez Roldán
Hospital Universitario Virgen del Rocío
SEVILLA

Araceli Beatriz Martín Antonio
Hospital Universitario Virgen del Rocío
SEVILLA

David Cano González
Hospital Universitario Virgen del Rocío
SEVILLA

F. Javier Padillo Ruiz
Hospital Universitario Virgen del Rocío
SEVILLA

Gracia Patricia Ortega Sáenz
Hospital Universitario Virgen del Rocío
SEVILLA

Guillermo Antiñolo Gil
Hospital Universitario Virgen del Rocío
SEVILLA

Ildefonso Espigado Tocino
Hospital Universitario Virgen del Rocío
SEVILLA

Inmaculada Pérez de Soto
Hospital Universitario Virgen del Rocío
SEVILLA

Irene Marcos Luque
Hospital Universitario Virgen del Rocío
SEVILLA

Joaquín Angel Quiralte Enríquez
Hospital Universitario Virgen del Rocío
SEVILLA

José Antonio Rodríguez Gómez
Hospital Universitario Virgen del Rocío
SEVILLA

José Ignacio Piruat Palomo
Hospital Universitario Virgen del Rocío
SEVILLA

José María Hernández Guisado
Hospital Universitario Virgen del Rocío
SEVILLA

José María Pérez Hurtado de Mendoza
Hospital Universitario Virgen del Rocío
SEVILLA

José Palacios Calvo
Hospital Universitario Virgen del Rocío
SEVILLA

Juan Miguel Guerrero Montávez
Hospital Universitario Virgen del Rocío
SEVILLA

Luis Manuel Jiménez Jiménez
Hospital Universitario Virgen del Rocío
SEVILLA

María del Pilar Gómez Garre
Hospital Universitario Virgen del Rocío
SEVILLA

Pablo Mir Rivera
Hospital Universitario Virgen del Rocío
SEVILLA

Patricia Ybot González
Hospital Universitario Virgen del Rocío
SEVILLA

Raquel Fernández García
Hospital Universitario Virgen del Rocío
SEVILLA

Rosario Pérez Garrido
Hospital Universitario Virgen del Rocío
SEVILLA

Salud Borrego López
Hospital Universitario Virgen del Rocío
SEVILLA

Teresa González Quevedo Tejerina
Hospital Universitario Virgen del Rocío
SEVILLA

Guillermo Izquierdo Ayuso
Hospital Universitario Virgen Macarena
SEVILLA

Inmaculada Sánchez-Matamoros Martin
Hospital Universitario Virgen Macarena
SEVILLA

Jesús Sánchez-Calero
Hospital Universitario Virgen Macarena
SEVILLA

Mª Carmen Garnacho Montero
Hospital Universitario Virgen Macarena
SEVILLA

María Jesús Pareja Mejía
Hospital Universitario Virgen Macarena
SEVILLA

Víctor Sánchez Margalet
Hospital Universitario Virgen Macarena
SEVILLA

Javier Miñano Sánchez
Hospital Universitario Nuestra Sra. de Valme
SEVILLA

Mª Carmen Delgado Jiménez
Hospital Universitario Nuestra Sra. de Valme
SEVILLA

Mª Reyes Gutierrez Tous
Hospital Universitario Nuestra Sra. de Valme
SEVILLA

Manuel Romero Gómez
Hospital Universitario Nuestra Sra. de Valme
SEVILLA

María Jover Cobos
Hospital Universitario Nuestra Sra. de Valme
SEVILLA

Alberto Machado de la Quintana
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Amancio Carnero Moya
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Eduardo Lissen Otero
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

José Villar Ortiz
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Juan Ureña López
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Luis Paz Ares
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Manuel Leal Noval
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Miguel Ángel Japón
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Rafael Fernández Chacón
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Alberto Pascual Bravo
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Alfonso Leal Cerro
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Ricardo Pardal Redondo
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Sonia Molina Pinelo
Instituto de Biomedicina de Sevilla (IBIS)
SEVILLA

Ana María Camean Fernández
Universidad de Sevilla
SEVILLA

Andrés Aguilera López
Universidad de Sevilla
SEVILLA

Ángeles Jos Gallego
Universidad de Sevilla
SEVILLA

Antonio Barrero Ripoll
Universidad de Sevilla
SEVILLA

Antonio Castellanos Mata
Universidad de Sevilla
SEVILLA

Antonio Grillo Reina
Universidad de Sevilla
SEVILLA

Antonio Ordóñez Fernández
Universidad de Sevilla
SEVILLA

David Pozo Pérez
Universidad de Sevilla
SEVILLA

Emilio Fernández Espejo
Universidad de Sevilla
SEVILLA

Fernando Monje Casas
Universidad de Sevilla
SEVILLA

Francisco Javier Vitorica Fernández
Universidad de Sevilla
SEVILLA

Hugo Galera Davidson
Universidad de Sevilla
SEVILLA

Ignacio Marín León
Universidad de Sevilla
SEVILLA

Javier Aznar Martín
Universidad de Sevilla
SEVILLA

Jerónimo Pachón Díaz
Universidad de Sevilla
SEVILLA

José López Barneo
Universidad de Sevilla
SEVILLA

José Manuel Romero Enrique
Universidad de Sevilla
SEVILLA

Juan José Toledo Aral
Universidad de Sevilla
SEVILLA

Julián Martínez Fernández
Universidad de Sevilla
SEVILLA

Maria Victoria San Martín Díez
Universidad de Sevilla
SEVILLA

Mercedes Fernández Arévalo
Universidad de Sevilla
SEVILLA

Ralf Erik Wellinger
Universidad de Sevilla
SEVILLA

Ricardo González Campora
Universidad de Sevilla
SEVILLA

Amalia Martínez Mir
Universidad de Sevilla
SEVILLA

Ana Paula Zaderenko
Universidad Pablo de Olavide
SEVILLA

Javier Salvador Bofill
Universidad Pablo de Olavide
SEVILLA

José Antonio Mejías Romero
Universidad Pablo de Olavide
SEVILLA

José María Pedrosa Poyato
Universidad Pablo de Olavide
SEVILLA

Juan Rigoberto Tejedo Huamán
Universidad Pablo de Olavide
SEVILLA

Ramón Pérez Cano
Universidad Pablo de Olavide
SEVILLA

Notes

Some researchers have multiple affiliations, and some of them may have even changed their affiliation, but they are assigned to the centre recorded in the databases of the Regional Ministry of Health's calls for subsidies for research projects. Furthermore, this list only comprises some of all researchers performing research lines in Andalusia in this field, and even includes people who are currently not active in research.

ANNEXE 4

RESEARCH PROJECTS RELATED TO ADVANCED THERAPIES FUNDED BY THE REGIONAL MINISTRY OF HEALTH OF THE ANDALUSIAN GOVERNMENT

GENETICS AREA

Analysis of genetic polymorphisms of molecules involved in innate immunity as prognostic factors of liver cirrhosis in patients co-infected with HIV/HCV.

Validation by RT-PCR of the genes selected after performing cDNA arrays of breast cancer samples obtained from a chemical carcinogenesis model induced by dMBA in Sprague-Dawley rats treated with adriamycin and hydroxytyrosol.

Analysis of the genetic variants of the entothelin gene and its receptors in relation to systemic sclerosis and its clinical manifestations, with special attention to pulmonary hypertension.

Genetic polymorphisms of the complement route and resistance to infection by HIV-1 in drug addicts by parenteral route.

Influence of the genetic polymorphism of hepatic transporters of drugs in the susceptibility of developing hepatotoxicity.

Pharmacogenomics and hepatitis C.

Role of methylation of microRNAs in the pathogenesis and prognosis of acute lymphoblastic leukaemia.

Genetic and functional study of the polymorphisms of Tlr and their relation to the etiopathogeny of inflammatory intestinal disease.

Impact of the genetic variants of susceptibility in the clinical condition in patients with chronic inflammatory diseases.

Application of microarray technology and mlpa for the identification of new loci related to genetically-caused mental retardation.

Study of cyclin D1 and cyclin D3 (positive cell cycle regulators), of geminin (protector of the genomic stability) and of fibroblastic growth factor receptor 3 (tyrosine-kinase receptor) as molecular biomarkers of carcinoma.

Epigenomic analysis of leukaemia-initiating cells in patients with acute lymphoblastic leukaemia.

Identification of genes susceptible to Multiple Sclerosis, by minisequencing on microarray supports.

Genomics of invasive infections by Aspergillus in patients with cancer. Analysis of genetic polymorphisms for the identification of genetic biomarkers which enable predicting susceptibility to infection and resistance to antifungal drugs.

Involvement of the intracellular signalling pathways mediated by the activation of Rac1 GTPase: a possible new therapeutic target for Fragile X syndrome.

Evaluation of candidate genes and analysis of genomic association for the identification of regions linked to Hscr disease and intestinal neuronal dysplasia.

Increased immunogenicity in tumoral cells after restoration of class i HLA expression by adenoviral vectors.

Genetic and epigenetic transcriptional regulation of the Prdm1 gene in lymphoid neoplasias.

Genetic basis of rejection mediated by specific donor antibodies in the transplant of solid bodies. Role of anti-glutathione S-transferase T1 antibodies.

Study of the impact of biological activity of Il-6 on transcriptional sensors of the lipid metabolism via two in vitro models: primary hepatocytes and differentiated foetal liver hepatocytes.

Genetic and environmental factors associated to non-affective psychosis starting in childhood and adolescence.

Development of a pharmacogenics unit in Hospital Virgen de las Nieves. Pilot test to individualize cancer therapies with monoclonal antibodies in clinical trial phase.

Impact of the mutation of the Von Hippel-Lindau (Vhl) gene, of the levels of hypoxia-inducible factors (Hif) 1α and 2α and of the polymorphisms of the VEGF gene and of its receptor in benefit of therapies to combat against VEGF receptor in patients C.

Characterization of new genes involved in cellular senescence: Establishing causality and its potential clinical application.

Identification of polymorphisms of genes related to the antioxidant defence system involved in obesity and Metabolic Syndrome in children of prepubescent age.

Role of the Line-1 retroelement in the molecular bases of Fanconi anaemia.

Loss of heterozygosity in chromosome 15 as a cause of alterations in HLA Class I expression which allows the tumour to evade the vigilance of the immune system.

Use of Caenorhabditis elegans as experimental model in the study of autism. Molecular mechanism of synaptic function.

Effect of variations in genes related to insulin resistance, lipid metabolism and inflammation on the postprandial state of patients with metabolic syndrome.

Analysis of the expression profile of microRNAs (miRNAs) in colorectal carcinoma: correlation to the response to chemotherapy treatment and to clinical evolution in patents with metastastic disease.

Study of the pattern of gene methylation in lung cancer and COPD.

Genetic evolution of the Ns5a region in the hepatitis C virus in patients subjected to several cycles of antiviral treatment.

Mitochondrial dysfunction in patients infected by HCV and/or HIV.

Molecular analysis of immune response to HCV.

Analysis of genetic polymorphisms associated to inflammation in cancer.

Candidate genes and Mediterranean diet: prevalence of Type 2 diabetes in Andalusia.

Molecular clinical study of Tremor-Ataxia Syndrome associated to Fragile-X and other movement disorders associated to Fragile-X syndrome.

Obesity, metabolic syndrome and Mediterranean diet. A hypothesis related to olive oil.

Study on the phenomenon of coexistence of mutations in the glucokinase gene, causing diabetes and monogenic hyperinsulinism, together with common polymorphisms in other genes causing insulin resistance.

Study of BDNF Val-66-Met polymorphism and other genetic factors in primary dystonia.

Protective action of L-carnitine in hypertensive nephropathy and cardiopathy.

Development of a liposarcoma model based on the transduction of the fus-chop fusion gene in human mesenchymal progenitor cells.

The hypermethylation of CPG islets in the promoter of the emp3 gene in human lines and glial tumours as a diagnostic indicator of survival.

Study of the gene expression profile for the diagnostic and prognostic assessment of patients with thyroid nodule lesions.

Identification of the alterations occurring in cells lines with respect to the tumours from which they were obtained, to improve their efficiency as tools in cancer translational research Implementation of quality policies.

Genomic/proteomic approach for the analysis of the physiopathological basis of suicide in mental disorders and drug abuse.

Analysis of the cellular and molecular mechanisms of response to treatment with new anti-tumour drugs and chemotherapy agents in acute myeloid leukaemia in relation to their specific molecular profile. Genomic and proteomic study.

Medullary thyroid cancer: Evaluation of candidate genes, analysis of genomic association to identify regions linked to the disease and characterization of miRNA expression profiles in tumours.

Characterization of the mutational spectrum of hereditary retinal dystrophies (HRD) in the Spanish population. Identification and functional characterization of genes responsible for HRD.

Study of the polymorphisms of the apoptosis-inducing ligand gene related to TNF (Trail) and of its receptors in patients with multiple sclerosis. Correlation with response to treatment with interferon beta.

Cell-gene therapy of Wiskott-Aldrich's syndrome by genetic surgery.

NANOMEDICINE AREA

Toxicological evaluation of carbon nanotubes in cells lines as a preliminary study of their potential medical use.

Study of rheological indicators of quality in new biomaterials for therapeutic use.

Preparation, evaluation and application of nanostructured dendrimer antigens and of minor determinants for the diagnosis of immediate hypersensitivity to beta-lactams.

Transportation by nanoparticles of the E gene and 5-fluorouracil-derivatives as new therapeutic strategy in advanced colon cancer.

Development of dendrimer structures with the capacity to include epitopes of allergens and immunomodulating molecules. Potential application of nanomedicine to vaccine development.

Synthesis and biological characterization of nanoparticles functionalized with vasoactive intestinal peptide (VIP) as a platform for innovative products in prostate cancer: immunoregulating and anti-tumour effects.

Development of nanoparticles for new selective therapies against cancer.

Dendrimer nanostructures supported on solid surfaces applied to the development of an in vitro test for the diagnosis of immediate hypersensitivity to beta-lactam antibiotics.

CELL THERAPY AND REGENERATIVE MEDICINE AREA

Derivation of stem cells to insulin production by hybridation with pancreatic islet cells.

Cell therapy in endothelial damage in patients, induced by chronic renal failure.

Isolation and culture of human stem cells for the generation of tissue replacements by tissue engineering. Evaluation of viability and cryopreservation in Tissue Banks.

Haematopoietic stem cells in a clinical study of patients with liver damage.

Role of ghrelin as promoter of pancreatic beta-cell proliferation in type 1 diabetes mellitus (Dm1).

Vascular calcification: experimental study of the phenomena of regression and repair in damaged artery walls.

Safety and efficacy of intra-arterial injection of autologous bone marrow stem cells in acute ischemic stroke.

Effect of the presence of pro-inflammatory cytokines on the proliferation and regeneration capacity of murine pancreatic islet beta cells. Regulatory role of the extracellular concentration of glucose.

Microencapsulation in gel for the selection of plasma cells secreting antibodies of interest in cell therapy with transgenic cells.

Role of Sam68 protein in the proliferation of preadipocytes and the differentiation of human adipocytes.

Myocardial regeneration after intracoronary implantation of autologous bone marrow stem cells in patients with acute myocardial infarctions with anterior localization.

Study of peroxisome proliferator-activated receptor alpha (PPAR-alpha) and its relation to cytokines compromised in hepatic regeneration. Clinical implications.

Role of PPARs in cell proliferation and differentiation: embryonic and adult stem cell models for analysing the potential of these nuclear receptors in regenerative therapies.

Role of the regeneration of pancreatic beta cells in type 2 diabetes therapy. Search for new therapeutic molecules.

Effect of β-cryptoxanthin on adipogenesic, angiogenesis and osteoblastogenesis. Application in the treatment of osteoporosis, obesity and in the prevention of the adverse effects of thiazolinediones used in the treatment of diabetes mellitus.

Effect of intracoronary infusion of bone marrow progenitor cells on myocardial regeneration in patients with dilated myocardiopathy. Clinical-biological study.

Role of Pttg1 protein in regulation of Dlk1 gene expression in proliferation and differentiation processes.

Transcriptional control during development of the pancreatic endoderm.

Adult mesenchymal stem cells (Msc). Differentiation to osteoblasts and adipocytes induced by drugs and plant biophenols. Their involvement in osteoporosis.

Research network of stem cells from umbilical cord blood.

Induced differentiation of stem cells as regenerative myocardial therapy.

Identification of mesenchymal stem cells in adult human peripheral tissues. Study of cell differentiation and possible therapeutic use and regeneration of joint lesions.

Study of gene expression levels in cultures of hepatocytes isolated from steatosic donor organs.

Characterization of miRNAs in murine and human embryonic lines: implication in cell differentiation.

Regeneration of insulin-producing beta cells.

Obtaining glomic cells from stem cells cultured for cell therapy for Parkinson's disease.

Application of generic engineering to developing high-efficiency human pancreatic islets and post-transplant survival.

Development of strategies for skeletal regeneration from mesenchymal stem cells.

Culture, differentiation, selection and characterization of cells differentiated from human embryonic stem cells derived from pre-embryos affected by genetic disease obtained after preimplantation genetic diagnosis.

Application of regenerative cell therapy to kidney failure: study in an experimental model.

Study of the potentiality of amniotic fluid stem cells in cell therapy and regenerative medicine.

Derivation of human embryonic stem cell lines derived from pre-embryos affected by genetic disease obtained after preimplantation genetic diagnosis.

Role of VEGF receptor 1 (VEGF- R1) blocking in obtaining insulin-producing cells from pancreatic stem cells.

Application of a muscular damage model to the study of the mobilization of progenitor cells to peripheral blood.

Comprehensive studies of epigenomics, microRNAs and gene expression to determine the best properties of pluripotentiality and self-renewal in the different sources of haematopoietic stem cells used in regenerative therapies.

Study of the homing of circulating progenitor cells towards ischemic heart tissue.

Multicentric, randomized, placebo-controlled, phase I/II clinical trial, to evaluate the safety and feasibility of therapy with two different doses of autologous mesenchymal stem cells from adipose tissue in patients with extensive chronic Graft versus Host disease.

Expansion of the human carotid body and phenotypical characterization for its use in cell therapy of neurodegenerative diseases.

Molecular characterization of stem cells from Her2+ breast tumours. Identification of possible diagnostic markers and therapeutic targets.

Heart regeneration model by mesenchymal stem cells transdifferentiated and transported by nanospheres.

In vivo and in vitro studies on the plasticity of adult stem cells in relation to damage induced in vascular calcification.

Study of the signalling by lysophosphatidic acid as biological modulator for its use in cell therapy with mesenchymal stem cells from adipose tissue in an experimental model of Multiple Sclerosis.

Pre-hematopoietic origin of Mllaf4 and Telaml1 translocations and hyperdiploidy in childhood leukaemia: development of a cell transformation model based on the use of human adult mesenchymal stem cells.

Optimization of culture conditions without "feeders" for human embryonic stem cell lines (cmeh) imported or derived from donor embryos in pre-implantation phase: differentiation of cmeh to haematopoietic line.

Therapeutic angiogenesis from autologous bone marrow in diabetic patients with critical peripheral ischemia. Comparison of mononuclear cells versus mesenchymal cells in vitro and in a murine model.

Role of endothelial cells and their angiogenic factors in obtaining insulin-producing cells from adult pancreatic stem cells.

Development of a Pro-B childhood lymphoblastic leukaemia model with Mll-Af4 translocation based on the use of human embryonic and umbilical cord stem cells.

Transplant of islets in Type 1 Diabetes.

Genetics and mitochondrial function in stem cell biology: development of new cell differentiation protocols with greater potential for cell therapies.

Notes

This list does not include the research projects funded by the Regional Ministry of Economy, Innovation and Science, or other public or private institutions.

ANNEXE 5

BIOTECHNOLOGY COMPANIES FROM THE BIOMEDICINE SECTOR INSTALLED IN ANDALUSIA

According to data provided by the Regional Ministry of Economy, Innovation and Science in December 2009

DSM DERETIL
Synthesis of b-lactam antibiotics: amoxicillin, ampicillin and cephalexin (head office in Barcelona)
Almeria

BIOORGANIC RESEARCH AND SERVICES, S.L. (BIONATURIS)
Biotechnology
Cadiz

CURAXYS
Production of therapeutic recombinant proteins in the field of follow-on biologics
Cadiz

LABORATORIOS PEREZ GIMENEZ,SA
Manufacturing of OTC drugs, generic drugs, health remedies and immunocosmetics
Cordoba

ALT RADICAL BI-TEC,SL
Search for new treatments in rare diseases
Cordoba

CANVAX BIOTECH,SL
Research and production of biological materials. Vaccines
Cordoba

VIVACELL BIOTECHNOLOGY ESPAÑA,SL (campus)
Research and production of biological materials
Cordoba

ABBOTT LABORATORIES, SA (Granada)
Manufacturing and development of nutritional products
Granada

BIOMASLINIC
Extraction and research on maslinic acid and hydroxytyrosol
Granada

FUNDACIÓN CENTRO DE EXCELENCIA MEDINA (MSD)
Innovative medicinal products
Granada

GENYCELL BIOTECH ESPAÑA, SL
Dist. of biotechnology products and development of diagnosis kits
Granada

INNOFOOD I+D+I, SL
R&D&i functional food from by-products
Granada

LABORATORIOS FARMACÉUTICOS ROVI, SA (Granada)
Manufacturing and research of pharmaceutical products
Granada

LORGEN GP, SL
Research and development of genetic diagnostic tests
Granada

MASTER DIAGNÓSTICA, SL
Research and production of clinical diagnostic kits
Granada

NEURON BIOPHARMA, SA
Development of drugs and research services
Granada

PULEVA BIOTECH, SA
Research and development of functional food
Granada

SANAVI, SA
Preparation of dietetic and dietary food
Granada

TRIANA SCIENCE & TECHNOLOGIE, SL
Development of protein crystallization boxes
Granada

VERBIOTECH I+D+I, SL
R&D&i of functional and dietetic food
Granada

VIRCELL, SL
Research and development of diagnostic kits
Granada

VITAGENES, SL
Research and development of genetic services
Granada

B-BRAUN MEDICAL,SA
Drug development
Jaén

ADP BIOTECNOLOGÍA
Development of biotechnology patents related to the biotechnology and life sciences areas
Malaga

CENTRO MEDITERRÁNEO DE FOTOBIOLOGÍA (CMF)
Use of new products extracted from algae which include UV factor, antioxidant and immunostimulating substances of interest for the cosmetics and pharmaceutical industry
Malaga

EURONUTRA
Research, development and marketing of new active ingredients, nutraceuticals and functional food, development of production engineering
Malaga

GENETAQ CENTRO DE BIOLOGÍA MOLECULAR
Molecular biology. Cancer research
Malaga

GERONIMO NATURE OIL, S.A. (GENOSA)
Research and development from oil, functional elements and cosmetic and pharmacy products
Malaga

VIVIA BIOTECH
Biotechnology company devoted to research into new indications of already existing drugs (reprofiling) in rare diseases
Malaga

BIODIS, SL
Dietetics
Seville

BIOMEDAL, SL
Development of new bioprocesses and tools for research, diagnosis and bioindustry
Seville

GENFIS, SL
Performance of functional and therapeutic studies of human pathology in animal models
Seville

INGENIATRICS TECNOLOGÍAS, SL
Use of technology platform applications for the smooth handling of fluids on micro and nanometric scales
Seville

NBT DIAGEN (NBT DIAGNÓSTICO GENERALES, SL)
Centre of human genetic diagnosis
Seville

NEOCODEX, S.L.
Genomic research in biomedicine for knowledge of the genetic and molecular basis of common diseases in humans. It has developed the largest private DNA bank in Spain
Seville

PEVESA PEPTONAS VEGETALES, SL
Design and manufacturing of hydrolyzed plant products
Seville

DENTAID, SL
Research, development and marketing of products for the prevention, diagnosis and treatment of diseases produced by dental plaque
Seville

GRUPO P-VALUE
Consultancy, development of R&D protocols, clinical trials
Seville

ANNEXE 6

TIME LINE

STRATEGIC LINES / ACTIONS	05-06/ 2010	07-09/ 2010	10-12/ 2010	2011	2012	2013	2014	2015
Prioritization and strategic forecast (line 1)								
1.1 Registration of research groups								
1.2 Identification of lines of knowledge to prioritize								
1.3 Assessment of lines by the Initiative's Advisory Committee								
1.4 Review of the classification of lines in the short and medium-term								
1.5 Trend Observatory								
1.6 Working group to analyse impact on the Andalusian Public Health System								

STRATEGIC LINES / ACTIONS	05-06/ 2010	07-09/ 2010	10-12/ 2010	2011	2012	2013	2014	2015
Knowledge generation and development of new therapies (lines 2-9)								
2.1 Network of Material Resources in research								
2.2 Directory of calls for subsidies								
3.1 End of construction and fitting out of monographic research centres								
3.2 Andalusian Biobank Network								
3.3. Special infrastructures								
3.4 Adapting the network of pharmaceutical laboratories								
4.1- 4.8 Researcher recruitment programmes								
5.1 Periodic basic and clinical researcher seminars								
5.2 Promotion of coordinated and multidisciplinary projects								
5.3 Research spaces, clinical and laboratories								
5.4 Plan for the communication of clinical trials in the SSPA								
5.5 Web space for collaboration between researchers								
6.1 Evaluation and dissemination of scientific and innovative capacity								
6.2 Stimulus and support for highly creative projects								
7.1 Coordination with Directors of the three Plans								
7.2 Promotion of preclinical research								
7.3 Web space for proposals of clinical trials in Advanced Therapies								
7.4 Creation of Technical Committee for Clinical Research								
7.5 Definition of criteria for starting CT and participation of centres								
7.6 Evaluation of CT proposal and participating centres								
7.7 Analysis of mechanisms for equal access to CT								
7.8 Adaptation of project calls to CT requirements								
8.1 Logistics support for performance of clinical trials								
8.2 Creation of restricted clinical trial forums								
8.3 Search for resources for manufacturing medicinal products and CT								
8.4 Advice on regulatory framework								
8.5 Organization of manufacturing process quality controls								
8.6 Product characterization and development								
8.7 Improvement of production systems								
9.1- 9.4 Development of funding policy								

STRATEGIC LINES / ACTIONS	05-06/ 2010	07-09/ 2010	10-12/ 2010	2011	2012	2013	2014	2015
Results transfer and application (lines 10-12)								
10.1 Analysis of protection level and freedom to operate in short-term lines								
10.2 Market studies on short-term lines								
10.3 Definition of prioritization and transfer mechanisms in short-term lines								
11.1 Market studies on medium/long-term lines								
11.2 Definition of prioritization and transfer mechanisms in medium/long-term lines								
11.3- 11.6 Technology watch / protection								
12.1-12.9 Promotion of social return								

STRATEGIC LINES / ACTIONS	05-06/ 2010	07-09/ 2010	10-12/ 2010	2011	2012	2013	2014	2015
Training (lines 13-15)								
13.1-13.3 Training of professionals manufacturing medicinal products in Advanced Therapies								
13.4 Training programme								
14.1-14.6 Training of researchers in Advanced Therapies								
15.1-15.2 Training in laboratory and people management								

STRATEGIC LINES / ACTIONS	05-06/ 2010	07-09/ 2010	10-12/ 2010	2011	2012	2013	2014	2015
Comunication action (lines 16-19)								
16.1 Information in the areas of healthcare and academia								
17.1- 17.3 Dissemination to the general public								
18.1 Collaborative seminars with scientific journalists								
18.2 Content in university journalism studies								
19.1 Patient Associations in Governing Committee								
19.2 Citizen participation forum								
19.3 Permanent information process to patients in the CT								
19.4 Participation of patients in communication activities								

STRATEGY AND ACTION PLAN 2010/2015

andalusian initiative for advanced therapies

ANDALUSIAN INITIATIVE
FOR ADVANCED THERAPIES
Servicio Andaluz de Salud
c/ Maese Rodrigo, nº 1, 1º Izq.
41001 Sevilla (SPAIN)
T **+34 955 019 040** · F **+34 955 019 019**
terapias.avanzadas@juntadeandalucia.es
www.juntadeandalucia.es/**terapiasavanzadas**

JUNTA DE ANDALUCIA