Andalusian Initiative for Advanced Therapies: Fostering Synergies

NATIVIDAD CUENDE

INTRODUCTION

The Iniciativa Andaluza en Terapias Avanzadas (IATA), which in English translates to the Andalusian Initiative for Advanced Therapies, was established to promote the development of new therapies to improve the population’s health and to incorporate innovative advanced therapies in the health care and progress of our region. To do this we seek alliances with the academic world, research institutions, health centers, patients’ associations, small and medium enterprises, and the pharmaceutical industry.

This requires us to identify, organize, and provide the support needed to maximize the development of multidisciplinary research in the field of advanced therapies in Andalusia. By facilitating the training of technologists and basic and clinical researchers, and by fostering translational research in this field—as well as promoting the generation of a business structure beneficial to such research—we hope to ultimately provide a source of wealth for the region and enable the potential benefits of advanced therapies to be passed on to the population in as short a time as possible.

The year 2009 was a critical period for IATA. We took this time to define our strategy and action plan for 2010–2015. This involved seven working groups, an advisory committee, and a governing committee composed of scientific leaders, clinical researchers, research managers, representatives from patients’ associations, and responsible parties from both the public and the private sectors.

The results map out a plan for the efficient orientation of resources and fostering of synergies among the fields of cell therapy and regenerative medicine, clinical genetics and genomic medicine, and nanomedicine. The plan also aims to facilitate the development of new therapies that will be offered to the population on the basis of equal access with maximum safety guarantees.

Building on Our Achievements

This plan is helping us build upon what I believe to be our main achievement to date, which has been to gather efforts from different public and private organizations and align them toward the same goal.

When it comes to our funding priorities in the area of stem cell research, using a standard of excellence as a baseline we fund projects involved in the whole development chain, from the bench to the bedside, whether they involve basic research, preclinical developments, clinical trials, or even technological transfer dossiers.

To raise funds for stem cell research we have tried to join efforts with all the available organizations and organisms that could enhance the field. In this sense, €72 million (U.S. $96.88 million) has been allocated to developing infrastructures associated with advanced therapies. The Regional Government of Andalusia has invested more than €25 million (U.S. $33.64 million), representing more than 35% of the total investment. The remaining resources were gathered from other Spanish public institutions, private funds, and European funds.

Besides this, another €51 million (U.S. $68.63 million) was invested during 2010–2011 in research, clinical trials, staff recruitment, training, and other activities. This financial milestone could not have been achieved without the collaboration of more than 20 public and private organizations and without the momentum from all the researchers involved.

By collaborating with multiple public and private institutions we have completed a network of thematic research centers and unique infrastructures, including the Andalusian Centre for Molecular Biology and Regeneration Medicine (CABIMER), the Andalusian Stem Cell Bank, the Pfizer-University of Granada-Junta de Andalucía Centre for Genomics and Oncology Research (GENYO), the Andalusian Cellular Reprogramming Laboratory (LARCEL), in collaboration with the Michigan State University, and the Genomics and Bioinformatics Platform of Andalusia.

In defining these thematic research centers, we sought to promote synergies encompassing those of the IATA: cell therapy, genetics, and tissue engineering. The centers also are intended to create a space that encourages public and private companies to collaborate on projects.
An inventory of the equipment and shared services reveals that our research support units and our partners from Andalusian universities currently provide a comprehensive portfolio of scientific services. Among them we find remarkable the Andalusian Public Healthcare System’s Bio-bank that coordinates and controls more than 400,000 biological samples, all fully characterized, registered, and suitably stored and available for use in research projects.

What is also true is that as part of the public health care system we are strongly committed to translational research. It is compulsory to implement some sort of bridge between promising basic stem cell science results and the clinical practice. Regarding this issue we proposed a clinical translation model for stem cells [1] in which manufacturing, clinical research, marketing, and organizational aspects are discussed.

Along with funding research, we support the advanced therapy field by being involved in any new legislation that might affect its research and clinical practices. European legislation on advanced therapies is quite recent, as well as quite complex in its implementation. The European Medicines Agency (EMA) periodically tries to establish discussion forums with stakeholders in which the IATA actively participates, and we also frequently work with the EMA’s Committee for Advanced Therapies.

**Taking It Bedside**

Another thing the IATA has done is to create a platform for technology maturation for investigational advanced therapy products. This platform supports translational research from the preclinical development stages to its transfer to the biotechnology sector or inclusion in the health system portfolio of services, with a special focus on clinical research.

We also provide logistical support for clinical trials of advanced therapy medicinal products. At present we are involved in 18 trials for different stem cell and tissue-engineered products, thanks mainly to the collaboration and commitment of clinicians from our public hospitals. This could not have been achieved without back office support during all phases of development.

The trials are set up in various clinical areas, including cardiology, neurology, immunology, hematology, peripheral vascular diseases, digestive, gastroenterology, and ophthalmology. To date, nearly 400 patients have been treated with different stem cell therapies, all under the strictest regulation.

To enable these cell therapies to be manufactured, a network of 10 Good Manufacturing Practice (GMP) laboratories was established in public hospitals, tissue banks, and research centers. To address the lack of experienced professionals in the field, the IATA created a Master’s in Manufacturing of Advanced Therapy Medicinal Products, a successful training program developed hand-in-hand with the University of Granada.

Over the past years we have been particularly active in the peripheral vascular disease field, performing six clinical trials and treating almost 200 patients, with promising results in reducing the risk of limb amputation. Besides winning many patients’ gratitude, we have been able to elucidate the main clinical clues and disease factors that improve the quality of life for patients affected by critical limb ischemia.

We cannot forget that a quarter of the people affected by this disease die before the end of the first year after its onset. Without a conventional pharmacological answer, stem cells seem to have great potential. The results we have obtained to date have encouraged us to promote a phase III clinical trial that hopefully will begin next year thanks to a collaborative agreement reached with a biotechnological company.

We are quite satisfied with several of the results obtained in our cardioiology clinical trials by a research team located in the Hospital Reina Sofia of Cordoba. The Cochrane Collaboration, an international not-for-profit and independent organization that provides the best evidence for health care, selected the team for several meta-analysis papers published.

We also are fostering clinical research into other diseases with a positive risk/benefit assessment or without clear therapeutic alternatives. This commitment has made us gather efforts for two clinical trials involving multiple sclerosis and another one for amyotrophic lateral sclerosis using mesenchymal stem cells.

Along with cell therapy and working to change the public’s view of the tissue engineering field, we recently received authorization for a clinical trial of artificial corneas generated from limbal stem cells, using a scaffold and technology developed by Prof. Antonio Campos of the University of Granada and his colleagues.

**Partnering for the Public Good**

Within a public research framework, international collaborations are nearly an obligation when facing the difficulties inherent in such complicated studies. With this in mind, we have established a partnership agreement with the California Institute for Regenerative Medicine as a collaborative funding partner. As a result, we partner with the University of California, Davis, specifically the teams of Drs. Jan Nolta and John Laird, in carrying out a phase I clinical trial using genetically modified stem cells [vascular endothelial growth factor-producing mesenchymal stem cells] for treating critical limb ischemia. This association implies a strong interaction in parallel with both the U.S. Food and Drug Administration and the EMA.

Under the leadership of Dr. Jose Cibelli, an expert in cloning and cellular reprogramming at Michigan State University, and Dr. Philip Horner from the University of Washington, we are also collaborating on the development of a new treatment for chronic spinal cord injury based on induced pluripotent stem cells. At present we are still in a preclinical stage, but we are working in parallel to validate the cell manufacturing protocols under GMP conditions in order to be able to start a clinical trial as soon as we overcome the regulatory hurdles.

By joining efforts with other research centers and hospitals we anticipate the creation of an in vivo and ex vivo gene therapy platform using somatic and stem cells. In collaboration with the Andalusian Public Healthcare System’s Technology Transfer Office, three license agreements have been established. In connection with these licenses, collaboration agreements have been reached with the companies for funding research groups.

**Looking to the Future**

From a knowledge generation perspective, we expect to increase by 25% the number of researchers and research groups in our advanced therapy activities, consequently enhancing the number of original articles published as well as the number of patents obtained.

We should be able to orchestrate these objectives by creating a business environment that fosters the development of advanced therapies, promoting efficient mechanisms of knowledge transfer and collaboration with the business sector. We
expect a minimum 10% progressive annual increase in the number of patents filed, patents licensed, and spin-off companies founded.

In 2014 we expect to start a phase III clinical trial and obtain marketing approval from the EMA in a 5-year time frame, as well as to start a second phase III clinical trial. These milestones should be accompanied by a progressive increase in the number of phase I and phase II clinical trials we promote over time.

**Fair and Equal Access**

From our point of view, along with developing therapies in the area of stem cells we cannot avoid our obligation to provide fair and equal access to the latest therapies to the whole population, so we deem it a strategic objective to be able to implement some of these treatments in the services portfolio of our public health care system under a cost-effectiveness basis.

Patient care is the *Leitmotiv* of our initiative. We had the opportunity to meet with many patients associations, which provided their points of view while our action plan was being designed. They also actively participated in the different working groups. As previously mentioned, we have a clear position on the need for a responsible risk-benefit analysis when it comes to using stem cell-based treatments for those disabling diseases that have no other clear therapeutic alternatives, as well as for offering these therapies under the strictest legal regulation.

We remain alert to institutions and companies that proceed without due rigor and responsibility in treating patients. Maintaining patient hope and trust is an immense responsibility, and any unethical behavior should be clearly identified and pursued. We must all contribute in protecting patients against unscrupulous companies, hospitals, or practitioners offering uncontrolled stem cell treatments. At the same time we are in fluid and continuous communication with the Spanish Medicine Agency, as well as the Spanish Transplant Organization.

Besides this cooperation with the competent authorities, we also participate in the Legal and Regulatory Affairs Committee of the International Society for Cellular Therapy and collaborate actively with other scientific associations. From our point of view, EMA recommendations should be reviewed in collaboration with scientific societies, taking into account organizational and economic consequences as well as recent scientific rationale [2].

We firmly try to apply our experience to further regulatory and clinical developments. The time required for developing a medicinal product is quite a bit longer than the time elapsed since our organization was founded, but we hope our efforts will contribute to improving the lives of patients suffering from various diseases.

Certainly, the 400 people already treated constitute our main inspiration.

*Editor’s note:* To learn more about the IATA’s Master in Manufacturing of Advanced Therapy Medicinal Products degree and the IATA itself, visit the organization’s website at [http://www.juntadeandalucia.es/terapiasavanzadas/en/home](http://www.juntadeandalucia.es/terapiasavanzadas/en/home).

**Meet Natividad Cuende, M.D., Ph.D.**

Dr. Cuende earned her M.D. and Ph.D. degrees in the area of family and community medicine, as well as in preventive medicine and public health, and she spent 6 years as a resident physician at different hospitals.

She has developed several research projects in the areas of sociological and health indicators and in cell and organ donation and transplantation. Her publishing credentials include about 125 scientific and technical papers, and she has presented at more than 80 scientific conferences and meetings.

With extensive teaching experience in the area of donation and transplantation of organs, tissues, and cells, as well as in public health and preventive medicine, Dr. Cuende includes in her duties the direction of the International Master Degree in Manufacturing of Advanced Therapy Medicinal Products, a program organized by the IATA in collaboration with the University of Granada.

**REFERENCES**

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