APPENDIX E: COLLABORATIVE FUNDING PARTNER OVERVIEW AND CONTACT INFORMATION: ANDALUSIAN INITIATIVE FOR ADVANCED THERAPIES (INICIATIVA ANDALUZA EN TERAPIAS AVANZADAS ("IATA")

THE FOLLOWING MATERIAL IN APPENDIX E WAS PREPARED BY THE ANDALUSIAN INITIATIVE FOR ADVANCED THERAPIES, SPAIN.

BACKGROUND

The Ministry of Health & Social Welfare of the Government of Andalusia has been developing different activities within the R&D Strategic Plan for Health. This has been the result of a clear commitment on the part of the Government of the Autonomous Region with Research and Innovation based on the conviction that Health Services that are intended to excel, should be linked to first-class biomedical research. Within this commitment arose the Andalusian Initiative for Advanced Therapies (IATA, from its name in Spanish, Iniciativa Andaluza en Terapias Avanzadas). Its mission 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. IATA will do this by seeking alliances between the academic world, research institutions, health centres, patients' associations, biotechnological SMEs and the pharmaceutical industry. In this framework, the Andalusian Ministry of Health & Social Welfare has promoted a number of agreements with both national and international academic and business institutions.

In 2010 a partnership agreement was signed between the California Institute for Regenerative Medicine (CIRM) and IATA through the Fundación Progreso y Salud (FPS). This agreement confirms the interest of both institutions to explore opportunities for collaboration in the field of stem cell research, among them the combined funding of collaborative research projects developed by research groups based in California institutions and groups that belong to the Andalusian Public Healthcare System (SSPA, from its name in Spanish, Sistema Sanitario Público de Andalucía). This research project funding takes part in CIRM calls named as RFAs (Request for Applications) published periodically. The purpose of the Andalusian Ministry of Health & Social Welfare is to be involved, through IATA supported by FPS, in co-financing collaborative projects of strategic interest for Andalusia. In order to do this, it is planned to publish regular calls integrating the requirements and

procedures of the RFA with those who are required by the Andalusian Ministry of Health & Social Welfare to achieve its goals.

The present call is published to reinforce the collaborative funding of Research Awards of the RFA "Disease Team Therapy Development III" no.13-01 that can be found on the CIRM website (www.cirm.ca.gov). Similar calls are expected to be published by the Andalusian Ministry of Health & Social Welfare for future CIRM calls where the Ministry could be interested in participating.

FUNDING AVAILABLE

The maximum amount of funding that IATA, through FPS, will assign for awarded Disease Team Therapy Development III Research Award projects will be of 3 million US $, covering total expenses of SSPA groups within those projects. It is anticipated that this will fund the participation of a maximum of 3 SSPA groups. The maximum amount budget per project for the research carried out in Andalusia shall not exceed 1 million US $.

BASIC REQUIREMENTS OF THE CALL

Subjective scope

The RFA 13-01 call "Disease Team Therapy Development III" provides the possibility to develop collaborative projects in which exists a shared leadership, with one Principal Investigator (PI) conducting part of the project in institutions or companies in California and another PI (Partner PI) developing part of the project within the Collaborative Funding Partner (CFP) entity, provided that they meet the eligibility criteria of CIRM and the CFP, respectively, in this case the Andalusian Ministry of Health & Social Welfare.

The potentially eligible beneficiaries of the funding from the Andalusian Ministry of Health & Social Welfare, through IATA and FPS, are those foundations or public entities answering to SSPA whose groups intend to carry out collaborative projects with groups belonging to California institutions or companies that meet the eligibility requirements published in the RFA to access CIRM funding, within the areas of interest listed below. Should groups from different provinces of Andalusia managed

by different entities intend to participate in the project, the application must be submitted by the entity that is anticipated to manage the major part of the budget. If the proposal includes a clinical trial mainly performed in Andalusia, the applicant and sponsor will be FPS.

Collaboration of groups and researchers not answering to SSPA, but based in Andalusia will be accepted only if the research developed in Andalusia is mainly conducted by SSPA groups, both in terms of finances and research activities.

Objective scope

Each funded Research Award´s key objective is to complete a clinical trial. This call will support research in a therapeutic candidate derived from or comprised of the following:

- A cell therapy derived from pluripotent stem cells
- Allogeneic adult stem cells or progenitor cells for repair and/or regeneration, except for those out of scope identified below
- Genetically- or pharmacologically-modified allogeneic adult stem cells or progenitor cells (e.g. hematopoietic stem cells) for repair and/or regeneration
- Tissue engineered (e.g utilizing a cell scaffold or biomaterial in combination with a stem or progenitor cell) functional tissues for implantation in vivo
- A small molecule or biologic demonstrated to target normal endogenous stem cells as the primary mechanism of action (MOA) (in vivo) for regeneration and repair
- Any therapeutic candidate developed under a CIRM Disease Team Research I (RFA 09-01) award

In case of disagreement with the research lines and requirements established in the final text of the RFA 13-01 “Disease Team Therapy Development III Awards” the aforementioned RFA 13-01 will hold priority (www.cirm.ca.gov).

Research period

The research period shall be for a maximum of four years.

Overall budget

Overall budget ceiling for each collaborative project (e.g. California and Andalusian portions taken together) can rise to 21 million US $, although the direct budget for

the research carried out in Andalusia shall not exceed 1 million US $ per project. Only in extraordinary cases is it expected that a project would be funded at the higher end of the range.

Services Paid for by the Regional Health Ministry

We offer the following services whose costs will be borne by our Regional Health & Social Welfare Ministry most of them through the Fundación Progreso y Salud who manages the Andalusian Initiative for Advanced Therapies' budget, in the cases in which the Fundación Progreso y Salud acts as the sponsor of a clinical trial:

1. Related to **clinical practice**: the network of public hospitals of Andalusia and primary care centers that provides health care to more than 8 million inhabitants. That includes: the utilization of the information incorporated in our digital medical records to identify the candidates for clinical trials, as well as all the costs associated with the clinical development of the trials (i.e. salaries of the nurses and doctors, hospital stay, any medical test or diagnostic procedure, medical and surgical treatments). The costs that will not be borne by the Andalusian Initiative for Advanced Therapies and that should be paid with the funds allocated to the research project involving a clinical trial are: insurance policies, data managers, monitoring and data analysis.

2. Related to **cell-based medicinal products**: fully equipped accredited laboratories to manufacture cell-based medicinal products following GoodManufacturing Practice (GMP). That includes: 9 laboratories with capacity to manufacture according to GMPs. One of these labs was designed specifically to manufacture cell-based medicinal products derived from iPS cells. Some of which could be available for the funded clinical trials. Running costs and maintenance of GMP facilities and salaries of personnel will be borne by the Andalusian Initiative for Advanced Therapies. The cost that will not be borne by the Andalusian Initiative for Advanced Therapies and that should be paid with the funds allocated to the research project supported by a specific GMP facility are: the validation costs to obtain the Medicine Agency's approval for that specific medicinal product, reagents and materials for production and quality control, shipping cost and any extra-equipment required according to the medicinal product, if/when applicable.

3. Related to the **management of Regulatory requirements**: the Andalusian Initiative for Advanced Therapies supports clinical trials through its expertise on:

- Guidelines of the European Medicine Agency (EMA) that apply to nonclinical studies, quality of cell-based medicinal products and clinical studies.
- GMP
- IMP Dossier draw up (USA: IND applications).
- Cell-based product characterization.
- Quality control determinations.
- Nonclinical studies.
- Design of clinical trials.
- Good Clinical Practice.
- Draw up of clinical protocol and researcher's manual.
- Safety vigilance of the IMP.
- Administrative release of medicinal batches.
- Authorization paperwork related to the GMP laboratory, the IMPD and the clinical trial required by Clinical Research Ethics Committees and the National Medicine Agency.
- Agreements with hospitals and clinicians.
- The cost that will not be borne by the Andalusian Initiative for Advanced
- Therapies and that should be paid with the funds allocated to the research
- project include the taxes related with the Regulatory Agencies, if there are any.

4. Related to **project management**: the Andalusian Initiative for Advanced Therapies through its management entity, Fundación Progreso y Salud (FPS), provides a project manager who is in charge of the management, accountability and economical justification of the clinical trial. Furthermore, s/he will help in the diffusion of results as well as the protection of any intellectual property that may be generated in the clinical trial. The project manager is supported by a wide range of specialists (part of FPS structure) in each of the required areas.

Application process

The Disease Team Therapy Development III Awards RFA 13-01 involves a two-step process. An eligible Californian applicant must first submit a Letter of Intent (LOI) to

CIRM. In the second step of the process, eligible applicants will submit a full application.

If an Andalusian research group is planning to collaborate with a California research group and participate in the Disease Team Therapy Development III RFA 13-01, the Andalusian applicant entity must submit a letter of intention to IATA (see contact details below) at least fifteen days before the full application date (set out in the RFA). In addition, the Andalusian applicant entity must submit to IATA the following documents in advance of this deadline:

- Standard application form (http://www.juntadeandalucia.es/fundacionprogresoysalud/gestionconvocatorias)
- Authorization letter signed by the principal of the Andalusian centers in which the project is planned to be developed.

If the research project is finally selected for funding by both, the Independent Citizens Oversight Committee (ICOC) of CIRM and the strategic scientific board designated by the Andalusian Ministry of Health & Social Welfare, the following documents are to be submitted by the Andalusian applicant to FPS (see contact details below) provided they are not already in possession of this entity:

a. Copy of certification of inscription in the corresponding public register.
b. Certified copy of the ID of the person holding the legal representation of the
c. Andalusian applicant.
d. Certified copy of the applicant's CIF (VAT-number).
e. Copy of the documentation of representation or empowerment of the legal representative.
f. Current original certificate of the Social Security obligations.
g. Ethics Committee certificate approving the research project.

Justification and ex-post evaluation

An annual justification is to be made to FPS by December 1st for each annuity of the project. The justification should comprise the following documents:

a. Brief report on performance of activities and results.
b. Comprehensive list of expenses identifying creditors, amount, payment date and the deviations over the approved budget if occurred.

Once the project is finished both a final technical report and a final economic report are to be sent to FPS within a term of no longer than 60 days. The final technical report must clearly explain the degree to which stated objectives have been reached. The final economic report must update the last annual report up to the end of the project.

Supporting documentation is to be sent together with the final economic report comprising original invoices or any other documents of equivalent probative value that are legally valid in tax declarations.

With the ex-post evaluation an analysis of the aims' achievement, efficiency in the project development and the relevance of results is expected. This will allow the funding entity to acquire knowledge that will improve its operations and enrich its decision making processes. Both positive and negative results obtained from the evaluation will be taken into account in assessing the provision of financing future calls.

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