

**AGREEMENT FOR THE CREATION OF AN
INTERNATIONAL RESEARCH PROJECT
(IRP)**

**“Exposome, genetics and cancer: the model of southern Brazil”
(EXPOGEN-CANCER)**

- The **Centre National de la Recherche Scientifique**, Hereinafter referred to as the “**CNRS**”, a public scientific and technological institution, with headquarters at 3, rue Michel-Ange 75794 Paris cedex 16, France, represented by its Chairman - Chief Executive Officer, Mr. Antoine PETIT, and by delegation of signature by Mr. Alain SCHUHL, Chief Research Officer,
- The **UNIVERSITE CÔTE D’AZUR**, Hereinafter referred to as the “**UCA**”, «UCA», a public scientific, cultural and professional institution with headquarters at, Campus Valrose, Grand Château, 28, avenue de Valrose, 06103 Nice cedex 2 (France), (France), represented by its President, Professor Jeanick BRISSWALTER,

CNRS and UCA, hereinafter referred together as The “Establishments”, acting jointly in their own name and on behalf of the « Institut de pharmacologie moléculaire et cellulaire (IPMC) » (UMR7275), directed by Mr Jean-Louis NAHON, hereinafter referred to as the "LABORATORY"

- The **ASSOCIAÇÃO HOSPITALAR DE PROTEÇÃO A INFANCIA DR. RAUL CARNEIRO**, Hereinafter referred to as the «**AHPIRC**», institution philanthropique with headquarters at Av. Desembargador Motta, 1070, Curitiba, PR, CEP 80250-060, Brazil, represented by its Président, Ety Gonçalves Forte, acting in its own name and on behalf of the three three divisions of the "PEQUENO PRINCIPE complex" (hôpital Pequeno Príncipe, Institut de Recherche Pele Pequeno Principe (IPPPP) and the Doctoral program in Biotechnology applied to child and adolescent health in the Faculty of Pequeno Príncipe (FPP).
- The **ST. JUDE CHILDREN’S RESEARCH HOSPITAL** Hereinafter referred to as the (SJCRH), a nonprofit medical corporation with headquarters at, 262 Danny Thomas Place, Memphis, TN 38105, (United States) represented by its CEO and director James R. Downing,

The Establishments, AHPIRC and SJCRH Hereinafter referred to jointly as the “Parties” or individually as the “Party”.

Whereas:

- The General Agreement for Technical and Scientific Cooperation between the Government of the Federative Republic of Brazil and the Government of the French Republic, signed in Paris on January 16, 1967,
- The Framework Cooperation Agreement between the Government of the French Republic and the Government of the Federative Republic of Brazil of 28 May 1996,
- The Scientific Cooperation Agreement between the CNRS and the CNPq signed on October 17, 1975 and renewed in Paris on May 11, 2007

PREAMBLE

The project is aimed to investigate how the interaction between genetic and environmental factors modulates cancer prevalence. These studies will leverage on the unique situation present in Southern Brazil, where the prevalence of a specific, low-penetrance germline mutation of the TP53 tumour suppressor gene is high in the population. However, the importance of our project far exceeds its application to a, though large, population in Latin America, since it will shed new light on the factors involved in determining cancer development in carriers of other low-penetrance TP53 alleles which are present throughout the world. The project relies on the long-lasting and fruitful partnership already established among the project participants since more than 15 years. Indeed, this IRP is part of the continuity of the collaboration initiated in the framework of the LIA NEOGENEX (2015-2018).

The participation of young investigators from all three partners will be essential for the success of the project.

Consequently, the Parties agree, on the basis of this Agreement (hereinafter referred to as the “Agreement”), to establish an “International Research Project - IRP” which is governed by the following provisions.

CHAPTER I – DEFINITION, CREATION, TERM, NAME, PURPOSE AND COMPOSITION**Preliminary Article – Definition:**

- **Agreement:** means this agreement for the creation of an international research project, its appendices and any amendments.
- **Background:** means any technical and/or scientific information and knowledge and / or any other type of information, in any form whatsoever, whether patentable or not and / or patented or not, and all the related rights, belonging to a Party or held by a Party prior to the effective date of the Agreement and / or developed or acquired by a Party outside the IRP as defined in Appendix N°1 "Program".

- **Results:** means any technical and/or scientific information and knowledge, patented or not, patentable or not, including know-how, plans, drawings, designs, software, formulae or any and all other type of information, in any form whatsoever, and all the related rights, that are developed as part of the IRP.

The Results are not considered confidential otherwise agreed by the Parties

- **Information:** All technical, practical, secret, substantial and identified information, which is formalised in any medium in the possession of any of the Parties and in particular any information, data, knowledge, samples, models, methods or processes, software, scientific and/or technical know-how, whether or not protected or protectable by an intellectual property right, as well as all information relating to financial affairs, commercial programmes, personnel, remuneration, strategy, agreements, assets, clients and competitors, made available to either Party, either during interviews, meetings or by the delivery of documents, letters or copies.

Article 1 - Creation and term:

The creation of the IRP shall be effective on January, the 1st, 2019 for a term of five years.

Article 2 – Name

The IRP is entitled “Exposome, genetics and cancer: the model of southern Brazil”
Its abbreviation is “EXPOGEN-CANCER”.

Article 3 – Purpose

The purpose of the IRP’s Agreement is to carry out the scientific program described in Annex 1 hereinafter “Program” which is an integral part of this Agreement.

Article 4 - Composition

The following laboratories and teams are involved in the IRP:

- Institut de Pharmacologie Moléculaire et Cellulaire (UMR7275) CNRS-UCA Director: Jean-Louis Nahon
- Hospital et Instituto de Pesquisa Pelé Pequeno Principe (IPPPP), Curitiba, Directot : Lucas Afonso Corrêa
- Division of Leukemia / Lymphoma Department of Oncology St. Jude Children’s Research Hospital (SJCRH), Memphis TN and its Chief: Jeffrey E. Rubnitz

Article 5 – Nature of the cooperation

The IRP is not a legal entity and has no legal capacity.

It is not the purpose nor effect of the Agreement, and nothing herein may be construed in this respect, to form, create, make effective or even acknowledge the creation of a joint venture, a company, and interest group or any other commercial group or entity, or a *de facto* company between the Parties.

CHAPTER II - ORGANISATION OF THE IRP

Article 6 – Scientific coordinators

The IRP is coordinated by two scientific coordinators. Scientific responsibility and management of the Program are assumed jointly by:

- Mr/Mrs Enzo Lalli (CNRS/UCA)
- Mr/Mrs Bonald C. Figueiredo (Hospital et Instituto de Pesquisa Pelé Pequeno Principe - IPPPP)- Associação Hospitalar de Proteção à Infância Dr. Raul Carneiro)

Together they shall coordinate the IRP's Program, the provisional budget and the annual financial and scientific reports to be submitted to the Steering Committee.

Article 7 – Steering Committee

7.1. Composition:

A Steering Committee is established and composed of :

- 6 members with entitlement to vote:
 - 2 Representatives of the CNRS:
 - The Director of the Institute INSB or his/her representative
 - The section of the National Research National Committee the CNRS coordinator belongs to.
 - 1 Representatives of the UCA
- 3 Representatives of the other Parties:
 - 2 Representatives of the Associação Hospitalar de Proteção à Infância Dr. Raul Carneiro
 - 1 Representative of the St. Jude Children's Research Hospital (SJCRH)

- Two persons from outside the IRP chosen by joint agreement between the Parties for their expertise, with an advisory capacity.

Each representative may be assisted by any expert at meetings of the Steering Committee, subject to the signing of a non-disclosure agreement. These experts attend in an advisory capacity.

The scientific coordinators of the IRP attend Steering Committee meetings in an advisory capacity.

7.2. Chairman:

The Chairman of the Steering Committee is appointed by and among its members on a revolving basis at each meeting.

7.3. Meeting:

The Steering Committee meets at least once a year at the initiative of its Chairman or at the request of the scientific coordinators as often the interests of the IRP need it.

The decisions of the Steering Committee are adopted by a qualified majority of three quarters (3/4) of its members, present or represented, each Party being represented.

Should it be impossible to physically hold a Steering Committee meeting, decisions of the Steering Committee may be adopted by teleconferencing or by written consultation.

7.4. Role:

The Steering Committee shall:

- give an opinion on the progress, program and direction of research;
- decide as to the budgetary resources required for the IRP's activities;
- report to the Parties on results obtained and approve the use of the financial resources.

It may also study all others matters relating to the IRP.

CHAPTER III – FINANCIAL AND HUMAN RESOURCES

Article 8 – Financial provisions

Every year, the provisional budget required to carry out the IRP Program shall be prepared by the scientific coordinators and shall be submitted to the Steering Committee for approval. This budget includes stated requirements as well as the corresponding resources, detailed by the Parties funding them.

Annex 2, which is an integral part of the Agreement, summarises the provisional budget for the first year of the IRP, which detail, in particular, the Parties' contributions and the suggested use of the funds. It is updated every year by a decision of the Steering Committee.

Each Party allocates and manages the budgetary credits corresponding to its own funding. There is no financial transfer between the Parties.

As well as these financial resources, each Party manages, under its own responsibility and own authority, and according to its own rules, all the resources which it provides pursuant to the IRP, notably: equipment, premises, facilities and staff.

Once a year, each Party shall justify to the other Parties, the resources actually allocated by each of them during the previous year (including equipment, premises and staff) in respect of the IRP. To this end, each Party draws-up a review of the financial resources allocated and their use (expenditure).

Use of the funding made by each scientific coordinator for the IRP Program may be verified at the year-end following an ordinary request from an authorised representative of the other Party. The credits used by each scientific coordinator for the IRP are subject to the usual controls in the respective countries so as to verify their compliant use in accordance with the Agreement.

Article 9 – Staff

The staffs solicited by the scientific coordinators to contribute to the Program shall remain fully attached to their home organisation and carry out their work on the basis of instructions from their superiors. The scientific coordinators discuss on the terms and conditions, schedule and scope of the involvement of these employees in the implementation of the Program. Annex 3 summarises this involvement for the first year of existence of the IRP. The Parties shall be immediately informed of any changes and Annex 3 be updated.

Use of the infrastructures and/or equipment by the Parties' staff is subject to compliance with the health and safety rules established by the owner Party.

For the purposes of the IRP, the staff of a Party may have access to the other Parties' premises, subject to compliance with the by-laws of the Party controlling the premises and possibly to the signing of a hosting agreement.

Article 10 – Partnership Agreements

The Parties consider on a case-by-case basis the conclusion of partnership agreements with third parties, the subject of which may or may not be related to the scientific program of the Agreement. The terms of negotiation, management and signature are defined on a case-by-case basis.

CHAPTER IV – INTELLECTUAL PROPERTY

Article 11 - Publications

11.1 Scientific results shall be published according to the usual custom and practice of the scientific community, subject to the application of the Confidentiality rules stated in the articles 11.2 and 12 of this Agreement.

Publications related to the work carried-out in common within the framework of the IRP shall mention the connection with the Parties of the IRP. They shall include the words ***“Research conducted within the context of the International Associated Laboratory “Exposome, genetics and cancer: the model of southern Brazil” (EXPOGEN-CANCER).***

11.2 Publication of the Results

Any and all publication or communication of the Results by either Party shall be subject, during the term of this Agreement and for two years after its expiry date or earlier termination, to the agreement of the other Parties which shall notify their written decision within two months of receipt of the draft publication at the latest. Thereafter and in the absence of an objection at the end of the said deadline (two months), agreement shall be deemed to have been given.

Consequently, all draft publications are referred for the opinion of the other concerned Parties which may remove or change certain information, the disclosure of which could compromise industrial and commercial use, under optimum conditions, of the results of the work carried-out in common within the IRP. Such removals or changes shall not compromise the scientific value of the publication.

If the information included in the publication or communication is required to be protected under industrial property, a Party may postpone the publication or communication for a maximum period of eighteen (18) months as from the date of the publication or communication request of the other Party.

Each Party agrees not to use the name, logo and / or trademark of another Party (and its laboratories) or any of its agents, in connection with the use or the exploitation of the Results arising from the Agreement, in particular for promotional purposes, regardless of the mean used (video, advertising brochure, press kit, etc.) without first obtaining the written agreement of the Party concerned.

Article 12 – Confidentiality

Each Party undertakes not to publish or to disclose, in any manner whatsoever confidential information of the others Parties, of which it may become aware during the negotiation and/or the performance of this Agreement. As such, the Background of a Party is a confidential information.

The Parties undertake to ensure that the information exchanged pursuant to the IRP and identified as confidential (hereinafter referred to as the “Confidential Information”):

- a) is kept strictly confidential and is protected to the same extent as their own Confidential Information;
- b) is only provided to their members of staff requiring knowledge thereof and is only used in application of this Agreement

Any and all other communication or use of the Confidential Information is subject to the prior and written authorisation of the communicating Party. Each Party undertakes to ensure that its staff referred to in section b) hereinabove comply with the provisions of this Agreement.

These provisions shall remain in force for a period of five years after the termination or early termination of the Agreement.

Notwithstanding the foregoing provisions, each Party is no longer bound by this commitment for Confidential Information for which it is able to prove:

- that it was in the public domain prior to its communication or subsequent thereto, but without any breach being attributable to it;
- that it was received legally from a third party;
- that it was already in its possession prior to the execution of the Agreement;
- that it was developed independently and in good faith by its members of staff who did not have access to said Confidential Information.

Moreover, these provisions may not preclude:

- either the obligation binding on all personnel involved in the Program to provide an activity report to its institution, such communication does not represent disclosure within the meaning of intellectual property legislation;
- or the defence of the thesis related to the Program of this Agreement, with such defence being organised whenever necessary so as to guarantee, in compliance with effective university regulations, the confidentiality of certain results of the works carried-out pursuant to the Program.

Nothing in this Agreement involves:

- a waiver, by the providing Party, as regards the protection of its information by any intellectual property right.
- an assignment or license, by the providing Party, of any right over this information for the benefit of the other Party.

It's up to the Scientific coordinators to determine which Results are considered as confidential and those that can be published.

Article 13 – Results and Background

13.1. Ownership of Results

The Results, whether patentable or not, which are obtained pursuant to the Agreement are the equal property of the Parties, hereinafter referred to as the “Joint Owners”.

Any Joint Results, likely to be protected by an intellectual property right or not, will be the object of a co-ownership agreement which will be established between the Parties before any direct and/or indirect, industrial and/or commercial, exploitation and in particular to:

- Organize the management of the co-ownership,
- Determine, where appropriate, the procedures for maintaining, extending and defending the Joint Results protected by an industrial property title,
- Define the areas as well as the legal and financial conditions of the direct and / or indirect industrial and / or commercial exploitation of the Joint Results.

As long as this co-ownership agreement has not been concluded, neither Party may take the initiative for the direct or indirect industrial or commercial exploitation of Joint Results.

Each Joint Owner retains ownership of the Background acquired by it before and/or outside this collaboration. The other Parties do not receive any rights on this Background as a result of the Agreement, subject to the right to use it solely for the purpose of the proper performance of the Agreement and for its validity duration.

If the exploitation of the Results by one of the Parties requires the exploitation of the Background held in whole or in part by another Party, the latter will endeavour, subject to the rights granted to third parties, to encourage such exploitation. The conditions of use of the rights of exploitation of the Background will be determined contractually on a case by case basis.

13.1.1 Use of the Results

Each Party may freely, and in a free of charge way, use the Joint Results for its own research and teaching purposes and in the context of research collaborations with third parties subject to the application of the Article 12 provisions (“Confidentiality”).

13.2. Appointment of an Administrator for the protection and exploitation of the Results

The Joint Owners designate among them an Administrator Institution (hereinafter referred as to “Administrator”) to be in charge of the protection and the exploitation of the Results, taking into account the expertise, the relevance of the intellectual property portfolio already owned by each Joint Owner.

Nevertheless, a French Party (hereinafter referred as to the “Mandatory”) is designated in accordance with the French law to represent the French Parties Joint Owners. The Mandatory will be able to rely on a third party to accomplish all or part of its missions according to existing contracts it made with this third party.

A co-ownership agreement will clarify and complete the rules organizing this point.

13.3. Protection of the Results by patent

Patent applications are filed by the Administrator in the joint name of the Joint Owners; the name of the inventor(s) shall be mentioned.

The Administrator has an express mandate from the other Joint Owners so as to manage the filing of patent applications and for obtaining and maintaining the resulting patents.

The Administrator assumes responsibility for steering and monitoring the priority filing procedures. It shall keep the other Joint Owners, represented by the Mandatory when appropriate, informed of the progress of the application and provides the list of foreign countries in which extensions shall be filed.

Should one of the Joint Owners waive entitlement to file or maintain a patent and/or part of the extensions effective, it shall advise the other Joint Owners, represented by the Mandatory when appropriate, thereof within a reasonable timeframe so that they may continue the procedure.

In addition, the waiving Joint Owner undertakes to sign or get signed all documents enabling the other Joint Owners to become sole owners of the said patent(s); the Joint Owners which continue with the procedure shall be the sole beneficiaries of any income generated by use of the patent in the countries for which the other Joint Owner waived entitlement to continue with the procedure.

The expenses relating to filing, the issuing procedure, keeping effective and extending patents (hereinafter designed as “Costs of intellectual property”) are supported by the Administrator.

A co-ownership agreement will clarify and complete the rules organizing this point.

13-4. Legal proceedings relating to patents

All the Joint Owners shall inform each other of any action for infringement by a third party against the Results, a declaration of invalidity, a claim or infringement of the Results by a third party.

All the Joint Owners shall act together to jointly agree on the strategy to adopt and shall supply each other with all the evidence in their possession permitting an evaluation of the nature of the dispute.

In the event of it not being possible to obtain a consensus, each of the Joint Owner may on its own and at its own expense take the actions which appear to it appropriate, it being understood that in this event, any compensation resulting from such actions ordered by the court shall wholly and irrevocably be the property of the Joint Owner acting.

A co-ownership agreement will clarify and complete the rules organizing this point.

13-5. Exploitation of the Results

The Administrator receives an express mandate from the other Joint Owners, to carry-out all exploitation-related work. In particular, it negotiates contracts on behalf of the Joint Owners with all companies wishing to exploit the Results.

The Administrator shall keep the other Joint Owners, regularly informed of the results of the negotiations. Any licensing agreement shall be signed by all the Joint Owners, represented by the Mandatory, when appropriate.

After deduction of the Costs of Intellectual Property from the incomes resulting from the exploitation of the Results, the Administrator shall repay to the Joint Owners, represented by the Mandatory, when appropriate a proportion of the royalties resulting from the exploitation of the Result(s), less a contribution to the exploitation expenses of the Administrator representing a maximum of 20% of gross incomes.

A co-ownership agreement will clarify and complete the rules organizing this point.

13-6. Software and databases

Each Party remains sole owner of the software and databases obtained by it outside the framework of the IRP (hereinafter referred as to “Prior software”).

Software created on the basis of Prior software in the context of the IRP (hereinafter referred as to “Derived software”) and which cannot be parted from the Prior software are the property of the Party owning the Prior software concerned, irrespective of who the author is. Thus where the Party which has made modifications to a Prior software is not the owner of said Prior software, it undertakes to assign exclusively the economic rights over the Derived software as and when they come into being to the Party owning the Prior software for no financial consideration for all countries and for the legal duration of the intellectual property rights.

However, if the Derived software are devised by the Party which is not the owner of the Prior software during the performance of this Agreement, the owning Party undertakes to grant to the Party which has developed the Derived software a licence to use said Derived software under terms which will negotiated in a separate agreement in good faith.

The new software and the new databases which are obtained in the framework of the IRP as well as the Derived software which can be parted from the prior software are the joint property of the Parties.

The Parties have a free and non-assignable right-of-use over this software and databases for the research purposes alone or with third parties. For databases, the right-of-use relates to both the structure and content and includes an extraction right.

CHAPTER V – MISCELLANEOUS PROVISIONS

Article 14 – Renewal – Assessment- Modification

Any modification made to the rules of the agreement must be the subject of an amendment.

The Agreement may be renewed by written amendment specifying in particular the purpose of the extension and the terms of its financing.

Article 15 – Adhesion, termination, withdrawal and exclusion

15.1. Adhesion

The Steering Committee may accept new laboratories or Parties in the IRP.

The adhesion of new Parties to the IRP requires the signing of an adhesion amendment to the Agreement and becomes effective on the date of such signature. Subject to a unanimous decision from the Steering Committee concerning the adhesion application, the Parties grant a mandate to the CNRS to sign the adhesion amendment in the name of all the signatory Parties of the Agreement.

All the Parties shall be informed of any new adhesion application (laboratory or Party).

15.2. Termination

In case of occurrence of an event owing to *Force Majeure* likely to jeopardize the execution of the Agreement, the Parties undertake to inform themselves, by sending a registered letter with acknowledgment of receipt, within ten (10) calendar days following the occurrence of this event, and to meet by any means (ex: Videoconference) as soon as possible to decide what action to take.

In the event of early termination of the Agreement, the Parties will meet to discuss, in particular, the fate of the IRP and its development.

In any case of termination of the Agreement, each Party undertakes to return to the other Party, at the request of the latter, all documents and other materials that it may have transmitted to it, without being able to keep any reproduction.

15.3. Withdrawal

Any Party may withdraw from the IRP with six (6) months' notice given by registered letter with acknowledgement of receipt. The Steering Committee shall approve the financial conditions of the withdrawal.

15.4. Exclusion

In the event of insufficient involvement in achieving the targets of the IRP or a Party's breach of its obligations, a Party may be excluded from the IRP by a unanimous decision of the Steering Committee; the concerned Party does not take part to the vote.

Article 16 – Liability

Each Party remains liable, without right of action against the other Parties, with the exception of cases of gross or intentional negligence, for repairing damage to its own property owing to, during the performance of this Agreement.

Should damage be caused to physical assets acquired by the Parties under this Agreement, the latter shall pay the repair or replacement charges for said assets on a pro rata basis of their respective financial contributions to the acquisition thereof.

According to the rules of ordinary law, each Party is liable for damage / loss of any nature caused to third parties during the performance of this Agreement.

Article 17 – Final provisions

The provisions of Chapter IV shall survive notwithstanding the expiry or termination of the Agreement or the withdrawal or exclusion of one of the Parties involved in this collaboration.

All research activities conducted in connection with the IRP shall be done in compliance with all the applicable laws, regulations, and guidelines of the countries and institutions in which the research is conducted.

The Parties shall endeavour to settle their differences out of court in an amicable way.

In the event of an unresolved dispute within a period of three months from the sending by a Party to the others Parties of a registered letter with acknowledgment of receipt stating the grounds for the complaint, the Parties may decide by joint agreement to terminate the Agreement before its term.

Should they fail to do so, any disputes may be settled before the defendant's domicile jurisdiction.

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CEO and Director

ANNEX 1:

PROGRAM

Our project is aimed to investigate how the interaction between genetic and environmental factors modulates cancer prevalence. These studies will leverage on the unique situation present in Southern Brazil, where the prevalence of a specific, low-penetrance germline mutation of the TP53 tumour suppressor gene is high in the population. However, the importance of our project far exceeds its application to a, though large, population in Latin America, since it will shed new light on the factors involved in determining cancer development in carriers of other low-penetrance TP53 alleles which are present throughout the world. Our project relies on the long-lasting and fruitful partnership already established among the project participants since more than 15 years. The participation of young investigators from all three partners will be essential for the success of our project.

Naturally-occurring genetic variation in the population plays a significant role in mediating individual responses to chemical and microbial exposure. It is largely unknown how chemicals used in agriculture (pesticides), released by industries, manufacturing byproducts, heavy metals and other substances can have a variable impact on population health. These interactions may be a major source of the heterogeneity in susceptibility to diseases, which in turn may also be related to specific agents of the exposome, isolated or in combination and involved in the aetiology of complex traits and diseases. The question where and how susceptibility to the environment is directly related to genetic variation will be an essential challenge of our project. The potential to perform large-scale studies in Southern Brazil offers unique opportunities to probe mechanisms underlying cancer development.

A specific variant of the *TP53* tumour suppressor gene (p.R337H) is present in the germline of the population of the States of the South and Southeast Brazil and in the bordering country of Paraguay with an exceptionally high frequency (average of 1 in 350). This huge frequency is linked to a founder effect responsible for the spread of the mutation within the population. The *TP53* p.R337H mutation is associated with various types of tumours and contributes significantly to the cancer burden in the regions where it is spread. It represents an important public health problem for a population of about 100 million people. This peculiar epidemiological offers an unprecedented option to investigate the influence of the exposome on cancer development in thousands of genetically predisposed individuals.

The objectives of our project are:

- To identify the genetic and environmental factors interacting with the *TP53* p.R337H mutation to influence cancer penetrance in Southern Brazil, where this genetic variant is present at a very high frequency and the exposome is variable and complex.
- To develop screening and clinical surveillance programs aimed to prevent, diagnose and treat cancer precociously in high-risk subjects identified by the previously mentioned studies.

Our project is positioned at the cutting edge of the international translational research on cancer. Our consortium is formed by renowned European, North and South American researchers and clinicians combining complementary expertise in the fields of cancer biology, genetics and clinics, epidemiology and environmental science. Our project has a strong innovation potential since it has the ambition to provide critical solutions to the problem of identifying individuals at high risk to develop cancer among the carriers of the *TP53* p.R337H mutation and to offer them to be enrolled in a personalized clinical surveillance program aimed to detect and treat cancer precociously. Furthermore, the importance of our project far exceeds its application to a, though large, population in Latin America, since it will very likely shed new light on the factors involved in determining cancer development in carriers of other low-penetrance *TP53* alleles throughout the world. The importance of those mutations to cause cancer is in fact increasingly recognized. Under this perspective, the possibility to study a large population of *TP53* mutation carriers in a

specific geographic region represents a tremendous opportunity to improve our knowledge about the genetic and environmental factors involved in modulating cancer penetrance in predisposed individuals.

ANNEX 2:

PROVISIONAL BUDGET FOR THE IRP FOR THE FIRST YEAR

Country	Institution	In-cash funding	Amount (€) (include detailed budget allocation if known)	In-kind input (if applicable)	Type of staff	Full-time equivalent OR person-months
France	CNRS	<input type="checkbox"/> Operations <input checked="" type="checkbox"/> Equipment <input checked="" type="checkbox"/> Mobility	15K euros		<input checked="" type="checkbox"/> Researcher	
					<input type="checkbox"/> Postdoc	
					<input checked="" type="checkbox"/> PhD	
					<input type="checkbox"/> Support	
	UCA	<input type="checkbox"/> Operations <input type="checkbox"/> Equipment <input type="checkbox"/> Mobility			<input type="checkbox"/> Researcher	
					<input type="checkbox"/> Postdoc	
					<input type="checkbox"/> PhD	
					<input type="checkbox"/> Support	
Brazil	AHPIRC	<input type="checkbox"/> Operations <input type="checkbox"/> Equipment <input type="checkbox"/> Mobility	20K		<input checked="" type="checkbox"/> Researcher	
					<input type="checkbox"/> Postdoc	
					<input checked="" type="checkbox"/> PhD	
					<input type="checkbox"/> Support	
United States	St Jude's Hospital	<input type="checkbox"/> Operations <input type="checkbox"/> Equipment <input type="checkbox"/> Mobility			<input type="checkbox"/> Researcher	

ANNEX 3:

COMPOSITION OF THE LABORATORIES / TEAMS AT 1 JANUARY 2020

COUNTRY	SIGNATORY Institution	UNITY / TEAM	STAFF	GRADE	Time devoted to the IRP %
FRANCE	CNRS-UCA	Institut de Pharmacologie Moléculaire et Cellulaire UMR7275	Enzo LALLI	DR	30
BRAZIL	Associação Hospitalar de Proteção à Infância Dr. Raul Carneiro	Hospital et Instituto de Pesquisa Pelé Pequeno Principe (IPPPP)	Bonald C. FIGUEIREDO		30
UNITED STATES	St. Jude Children's Research Hospital (SJCRH)	St. Jude Children's Research Hospital (SJCRH)	Raul C. RIBEIRO		20