Presentazione dei progetti finanziati da FRRB nell'ambito della Call JTC 2016

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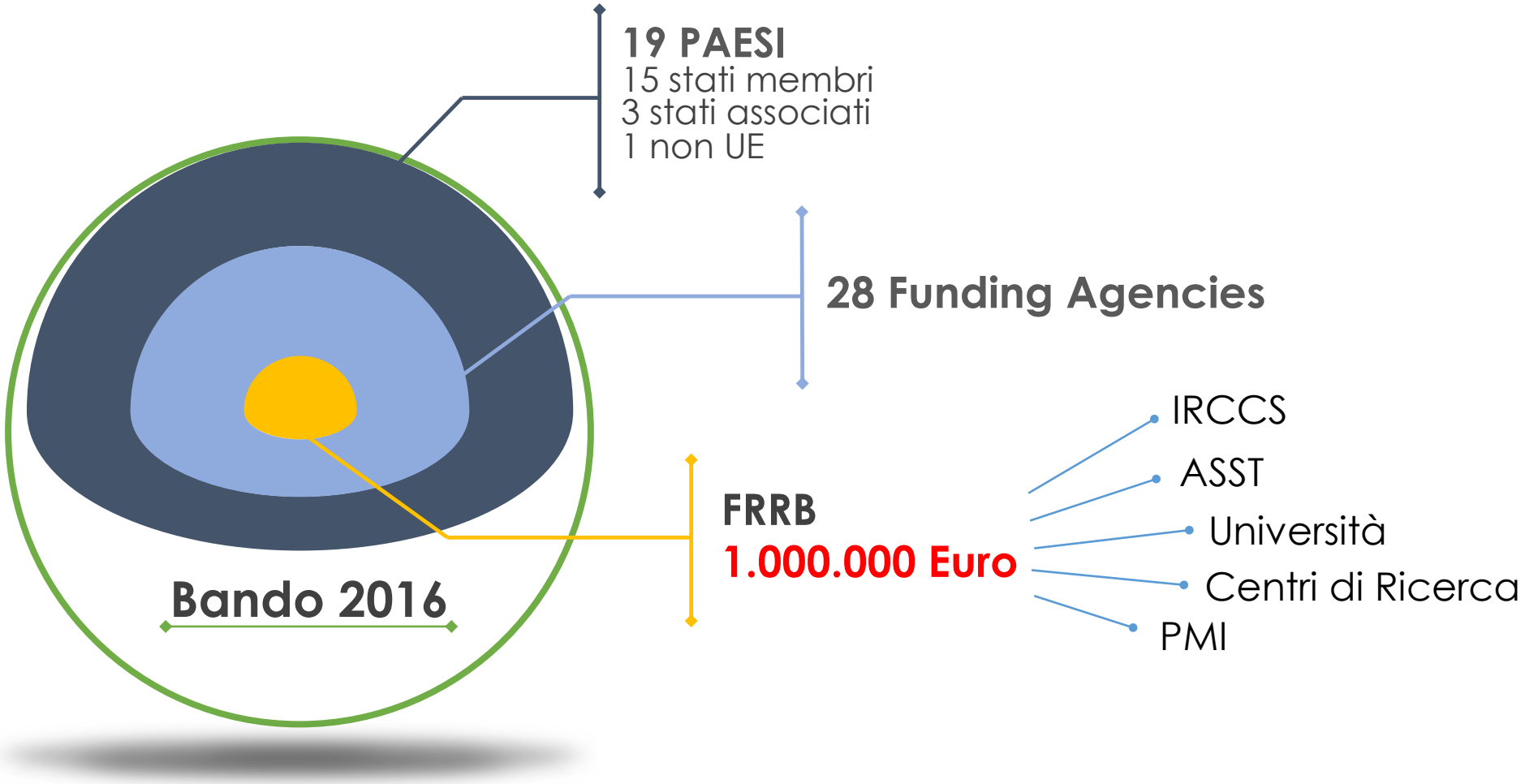
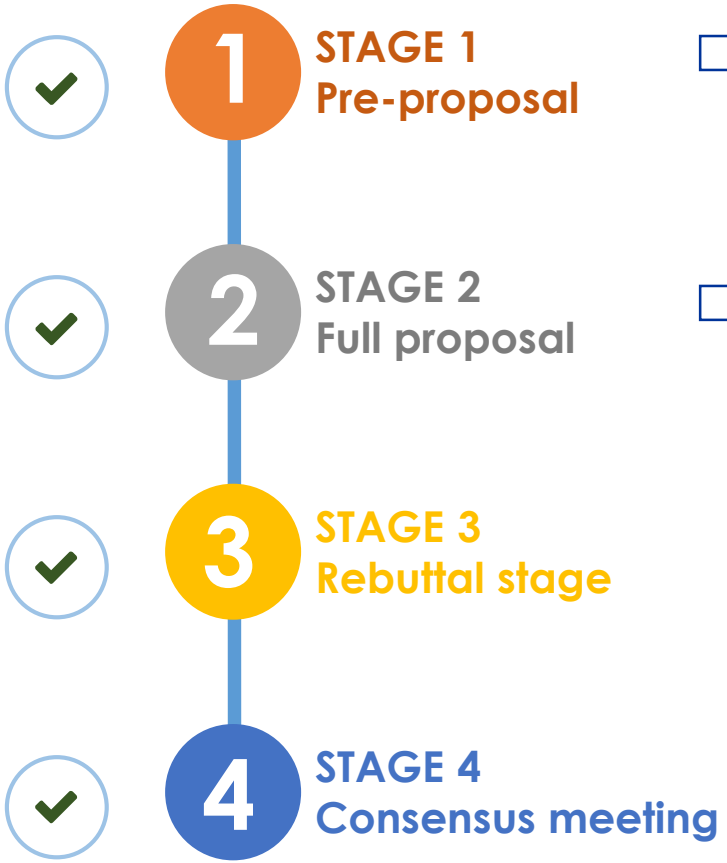
Fondazione Regionale per la Ricerca Biomedica

Bando TRANSCAN-2 JTC2016

Minimally and non-invasive methods for early detection and/or progression of cancer



Processo di Revisione



9 projects

5 projects

3 projects

Evaluators of full proposal:

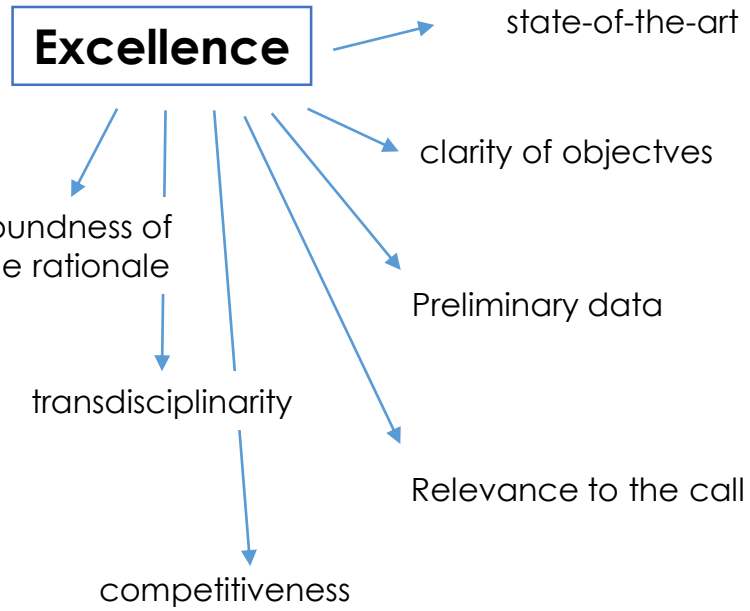
SEC member 1
SEC member 2
Ext reviewer

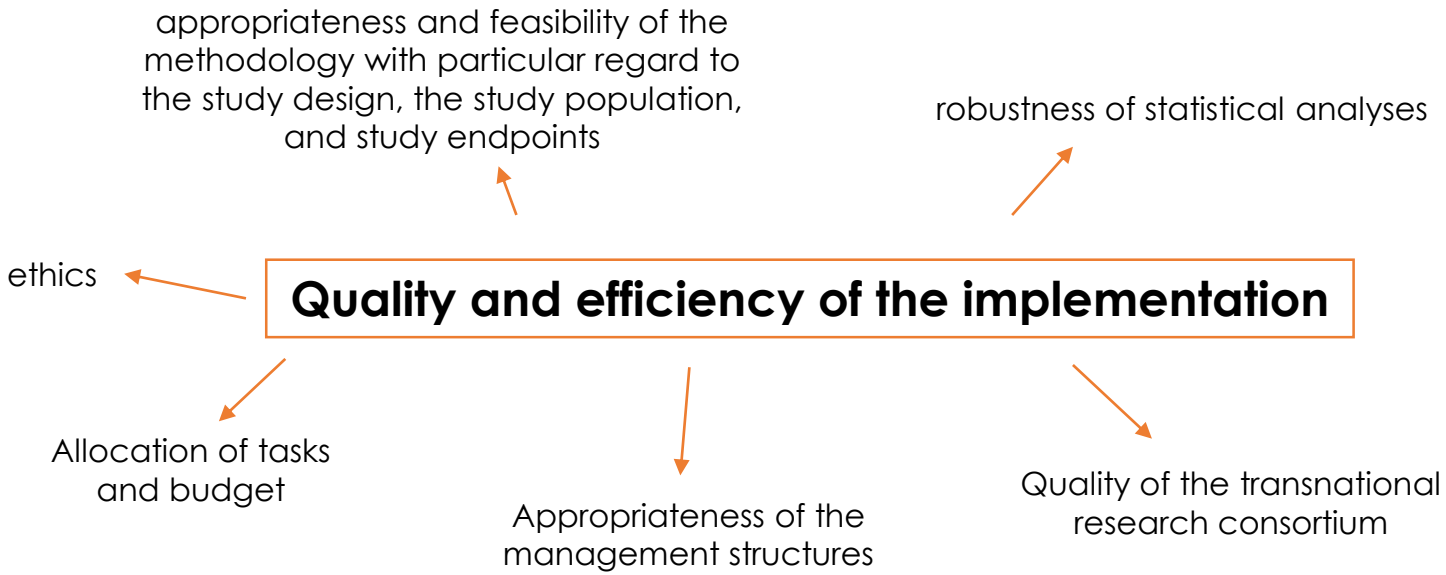
SEC methodologist
Ext methodologist

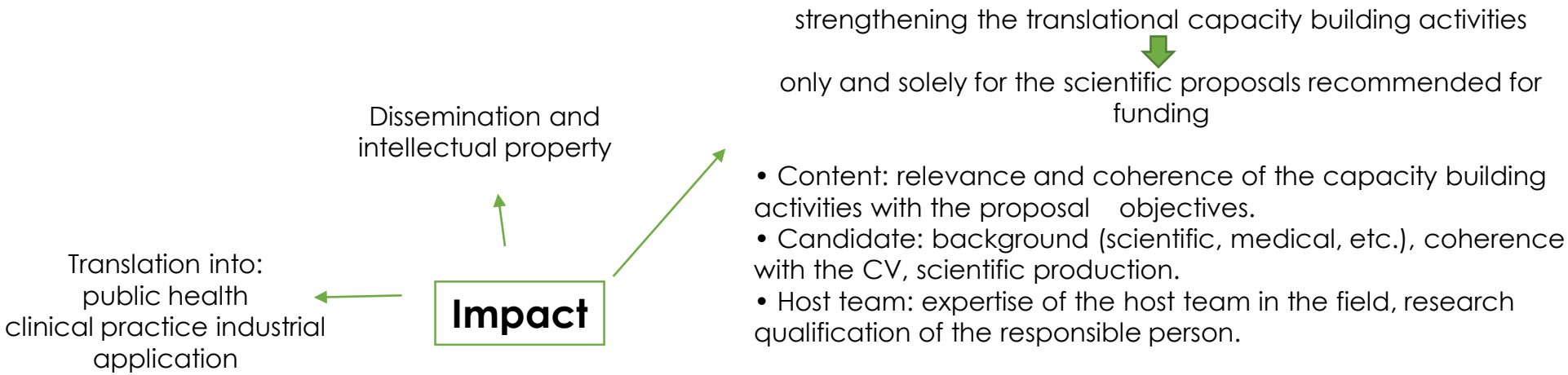
TRANSCALL-2

iMMunocell

SCRAtCH


Excellence
Advancement beyond state-of-the-art
clarity of objectves
Preliminary data
Relevance to the call
competitiveness
transdisciplinarity
Soundness of the rationale


Quality and efficiency of the implementation
appropriateness and feasibility of the methodology with particular regard to the study design, the study population, and study endpoints
robustness of statistical analyses
ethics
Allocation of tasks and budget
Appropriateness of the management structures
Quality of the transnational research consortium


Impact
Dissemination and intellectual property
Translation into:
public health
clinical practice industrial application
strengthening the translational capacity building activities
only and solely for the scientific proposals recommended for funding
• Content: relevance and coherence of the capacity building activities with the proposal objectives.
• Candidate: background (scientific, medical, etc.), coherence with the CV, scientific production.
• Host team: expertise of the host team in the field, research qualification of the responsible person.

TRANSCALL-2

Integration of genetic biomarkers and early Minimal Residual Disease to improve risk stratification and cure in childhood Acute Lymphoblastic Leukemia.

Consortium members:

1. **University of Milano Bicocca, Italy – Prof. Andrea Biondi COORDINATOR**
2. **ASST Monza, Italy – Prof. Alberto Piperno**
3. Hannover Medical School, Germany – Martin Stanulla
4. University of Heidelberg, Germany – Martina Muckenthaler
5. Sheba Medical Center, Israel – Shai Izraeli
6. Univeritè Paris Diderot, France – Helene Cavé

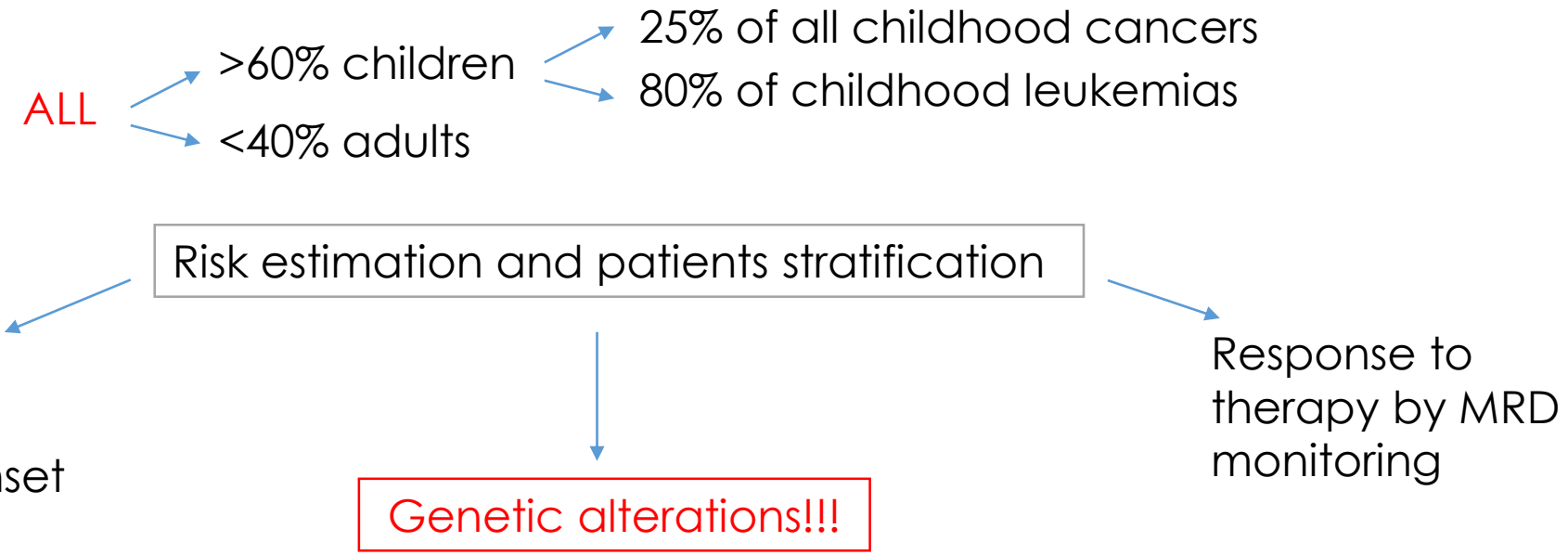
Total requested funding: 1.485.568 → total funded by FRRB: **464.996**

Evaluation:

Reviewer 1: the project has a solid workflow, good organization of the work projects and it is based on a skilled collaboration among several European partners. Impact in the state the art and translational aspect are evident.

Reviewer 2: built on the expertise of the cooperation of the existing consortium that have lead to remarkable revolution on risk stratification and therapeutic adjustment for patients with ALL. Appropriate methodology and high potential impact.

Reviewer 3: innovative project with a well-designed study plan by a highly experienced team of experts within the field. Potential to provide meaningful and insightful impact to both clinical and research fields.



Aim of the project: use minimally invasive methods to screen childhood leukemia population for new molecular markers at diagnosis.

- Identify new subgroups
- Improve risk stratification
- Improve clinical decision making for a more personalized and evidence-based treatment

AIM 1: identification of new genetic subgroups in childhood ALL

WP1

Develop methodological guidelines for validation of biomarkers and MRD analyses.

- TRANSCALL
- New protocols
- Methodology for multiplexing information

PARTNERS 1,2,3,4,5,6

WP2

Detect new abnormalities in **BCP-ALL** patients treated with updated protocols and assess their biological significance, according to selected biomarkers in WP1:

- Kinase fusion genes
- CRLF-JAK-STAT aberrations
- MEF2D-rearranged cases
- Deregulation of DUX4 and ERG
- ZNF384 fusion genes

PARTNERS 1,2,3,5,6

WP3

Detect new abnormalities in **T-ALL** patients treated with updated protocols and assess their biological significance.
Validation of these new biomarkers will be performed similar to WP2

PARTNERS 2,4,6

WP4

Dissect the subclonal composition of BCP- and T-ALL and their biological significance, which is currently unknown.

PARTNERS 1,2,3,5,6

AIM 2: Explore the feasibility and transferability of current standards to less invasive methods

WP5

1. Measurement of cell free DNA in serum of patients compared to DNA in circulating blasts
2. Analysis of biomarkers from serum samples compared to standard protocols to evaluate MRD

PARTNERS: 1,2,3,5,6

iMMunocell

Single-cell immunophenotypic and transcriptomic profiling for minimally-invasive detection of early multiple myeloma.

Consortium members:

1. Fundaciòn para la Investigaciòn Medica Applicada, Spain – Jesus San Miguel COORDINATOR
2. **ASST Spedali Civili Brescia, Italy – Dott. Aldo Maria Roccaro**
3. Universitàtsklinikum Heidelberg and HUMC, Germany – Harmut Goldschmidt
4. IUC Oncopole, France – Hervè Avet-Loiseau

Total requested funding: 1.106.356 → total funded by FRRB: **432.259**

Evaluation:

Reviewer 1: excellent project, very well designed and structured, with the potential to have a very significant clinical impact. Impressive record of publications and scientific projects awarded by the team and positive impact of previous collaborations.

Reviewer 2: excellent project, well written and carefully planned. It is expected to have strong clinical and scientific impacts.

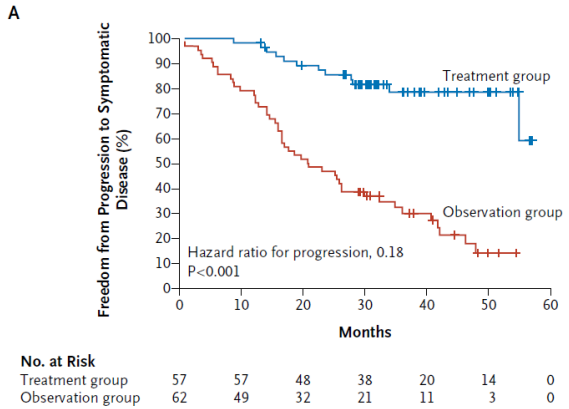
Reviewer 3: the potential clinical impact of this project is high, excellent clinical environment, very well described with a convincing implementation plan.

Most patients relapse and become refractory to all available drugs → **MM is largely incurable!**

Current approach: no treatment of premalignant conditions (MGUS, smoldering MM) until symptomatic disease develops

Patients are stratified according to the probability of malignant transformation → Around 40% of SMM patients are considered
HIGH RISK

Early treatment have been shown to be effective



Patients subgroups are defined by predetermined population-based criteria and not according to truly patient based approaches

Aim of the project:

- Improve patient stratification to avoid a 20% unnecessary treatment and include previously excluded subgroups
- Use more effective (immuno)therapies to avoid malignant transformation

Mateos MV et al. N Engl J Med. 2013 Aug 1;369(5):438-47. doi: 10.1056/NEJMoa1300439.

Aim 1: determine with single-cell resolution how the epigenome and the transcriptome of tumour cells evolve from stable to progressive disease

Patients need to be tested periodically and this requires minimally invasive methods

San Miguel's group: genetic and molecular featurer of BM plasma cells are the same as Circulating Tumor Cells

Aim 2: evaluate every 6 months <u>in blood samples</u>

- role of CTCs numbers
- mutations in cell free DNA
- content of exomiRNAs → transfer of miRNA within exoxomes from MSC to PC contributes to disease progression

To predict risk of malignant transformation

Aim 3: define the immune signature of SMM related to disease stability or progression by monitoring patients every 6 months in blood samples and every year in BM samples.
A bionformatic analysis will be performed to compare their immune signature to the one of healthy patients.

SCRAtCH

Microbiota-based screening of anal cancer in HIV-infected individuals.

Consortium members:

1. Ramon y Cajal research institute, Spain – Sergio Serrano-Villar COORDINATOR
2. **ASST Santi Paolo e Carlo, Italy – Dott.ssa Camilla Tincati**
3. University of Hohenheim, Germany – Jana Seifert
4. Oslo University Hospital, Norway – Marius Troseid
5. Agencia estatal consejo superior de investigaciones cientificas, Spain – Manuel Ferrer

Total requested funding: 734,279 → total funded by FRRB: **89.652**

Evaluation:

Reviewer 1: The project is very well designed and the methodological part is robust and mastered. Expected results would have a high impact on patient care and follow-up by improving current strategy for anal cancer screening. The consortium is well-built and includes all the expertise needed to carry out the project.

Reviewer 2: Project with an interesting hypothesis focussing on bacterial properties of anal cancer patients. Could allow for new screening method.

Reviewer 3: Relevant and well-developed project proposal

Anal cancer is 40 to 130 folds increased in HIV infected subjects

MSM

Persons with a history of anogenital condylomata

Women with abnormal vulvar of cervical histology – > HPV oncogenic transformation

Current strategy: anal cytology

- normal = repeated after 12 months
- abnormal = high resolution anoscopy
  - 95% sensitivity vs 58% specificity
  - overwhelming for health resources
  - Invasive

<u>Need to improve the screening system</u>

- Emerging evidence support the concept that intestinal bacteria might amplify or mitigate carcinogenesis
  → candidate bacteria biomarkers of pre-cancerous lesions have been identified in MSM
- In HIV women, cervical bacteria have been implicated in HPV associated pre-cancerous lesions

Aim of the project: combine anal cytology with analysis of bacterial biomarkers in anal epithelium to improve the screening for anal cancer in high risk population

Aim 1: identify in HIV infected MSM a set of anal-associated bacterial biomarkers to improve the accuracy of anal cytology

- species
- proteins
- metabolites

Aim 2: externally validate the diagnosis accuracy of microbiota based screening

Aim 3: generate a model linking bacteria to proteins and metabolite fluxes in order to

- Identify potential targets of intervention
- Dissect the mechanisms implicated in anal cancer and HIV infected individuals

Thank you!

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