

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2019

Project: UNRAVELLING THE CROSSTALK BETWEEN LIVER IMMUNOLOGY AND OXIDATIVE STRESS: A NOVEL PARADIGM IN HEPATIC FIBROSIS

Applicant: De Martin Sara

Giudizio Commissione Esterna

General assessment of scientific quality and innovation

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*
- *Has the project the character of start-up research that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

It is an interesting project, quite original and anchored in the hepatochemistry know-how and addressing an important problem. Therefore, it has a potential to attract funding and broad collaborations.

Reviewer n. 2

The project aims at expanding the knowledge on the role of NOXs for immune system regulation. Positive results will allow submitting grant applications and possibly attracting funds for further investigation that could result in new pharmacological approaches to fibrosis.

Reviewer n. 3

The validation of the research hypothesis will have high impact for both basic and translational science. The existence of this putative mechanistic link between NOXs and liver fibrosis will provide a novel target for new therapeutics and, therefore, has the potential for start-up activities and development of follow up studies.

Reviewer n. 4

Role of NOXs in hepatic fibrosis and the immune response, through co-culture and in vivo experiments and using NOX inhibitors.

Although the role of the inhibitor GKT137831 has been in vivo investigated in hepatic fibrosis (Aoyama 2012; Jiang 2012), the relation of adaptive/innate immunity with NOX-mediated fibrogenesis is not clear.

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Is the project supported by adequate human resources (young scientists, PhD students, etc.)?*

Reviewer n. 1

The plan appears over-ambitious. The development and validation of the in vitro model would be a worthy project in its own rights but also very difficult to accomplish. To reproduce in vitro the interplay between different cells in situ is a holy grail of biomedical studies, which proves elusive. Some preliminary data would be helpful.

The in vivo studies are straightforward but time consuming, especially that two models are to be compared.

Finally, identification of phenotypic changes in isolated cells may produce data different to what happens in situ, unless NOX inhibition causes long-lasting imprinting. Is there any evidence for this?

Funding for a post-doc has been requested although it appears too low to cover the entire period. Top-up for consumables might be required and there are commercial grants that may be used for that purpose.

Reviewer n. 2

The rationale of the project is clearly described. The same is true for the activities that will be carried out. Critical to the project's success is the recruitment of a post-doc with appropriate expertise. The applicant allocated a suitable budget for this.

Reviewer n. 3

The evidence underlying the formulation of the hypothesis linking NOXs to liver fibrosis is not clearly expressed. The information provides plenty of information that should be better structured or streamlined to facilitate the reader in understanding the rationale of the proposal.

Reviewer n. 4

One postdoctoral researcher is foreseen.

The PI does not indicate an approximate number of mice which will be included in the study, although there is ethical approval. Why is task 2 (in vivo experiments, month 3-15) not started at month 1?

There could be problems with the co-culture experiments (as described in risks). It would have been helpful to know if other groups have been successful in such co-cultures (no reference included).

Inhibitors that will be used are not described (a pair mentioned in state of the art, but not known if they will be the ones used) and it would have been necessary to search for the corresponding bibliography as information.

Competence and expertise of the applicant.

- *What are the merits and scientific expertise of the applicant?*
- *Are they appropriate and sufficient for the proposed project?*

Reviewer n. 1

Very good and in the right area. A prolific author.

Reviewer n. 2

The applicant's publication record witnesses the scientific expertise on the topic of the project. The applicant can rely on collaborations with experts in different fields, either Italians or foreigners. Therefore, no issues are foreseen for a smooth advancement of the project.

Reviewer n. 3

The applicant has an international profile and adequate scientific production. She is senior/corresponding author in several articles and has developed a qualified research profile.

Reviewer n. 4

Good publication record and broad experience related to the topic, for the missing experience, there is support by experts in the field.

Competence and expertise of the research team.

- *Does the research team bring complementary expertise to the project?*
- *Is the project involved in international research collaborations that can significantly contribute to the success of the project?*

Reviewer n. 1

Excellent, with significant complementarity of skills and some international connection.

Reviewer n. 2

The collaborators of the applicant bring the expertise that is needed for successfully completing project's activities. An international collaboration is in place.

Reviewer n. 3

Fundamental international collaborations are not planned.

Reviewer n. 4

Very good team of collaborators (national) and one international collaborator but not included in the project.

Overall assessment

- *Strengths and Weaknesses*

Reviewer n. 1

It is an interesting idea but the experimental approach appears too broad and not supported by sufficient preliminary data.

Reviewer n. 2

S – The applicant has gathered a team of experts in different fields important for a smooth progression of the project.

S – The combination of in vivo and in vitro approaches is important for the success of the project.

W – Task 1 is very challenging. Failure to obtain an in vitro model would compromise the possibility of testing compounds with potential therapeutic application in a simple assay set up.

Reviewer n. 3

Weakness: Research hypothesis and rationale of individual tasks should be streamlined and clearly presented

Strengths: Established set of methods and adequate internal collaboration and expertise. High impact milestone delivery.

Reviewer n. 4

The PI mentions that the co-culture experiments might be a problem. These models exist. A deeper description and some references might have shown that the model and the inhibition experiments are feasible.

Experience of the PI and the team very good.

Minor comment: list of bibliography missing, not known which inhibitors and how many animals will be used.

Giudizio Commissione Interna

Il progetto è ben presentato ed articolato e gli obiettivi finali sono chiari e definiti. I tasks sono ben descritti. La tematica affrontata si colloca in un'area della Farmacologia di particolare interesse scientifico ed è coerente con le linee di sviluppo del Dipartimento.

Il profilo scientifico del proponente è appropriato ed è evidente il contributo nello svolgimento dell'attività scientifica prevista dal progetto. Il team è ben organizzato nei diversi ruoli che sono definiti per tutti i componenti. Appaiono interessanti e complementari le sinergie con ricercatori di altri Dipartimenti della Scuola di Medicina dell'Università di Padova.

Il PI cita la presenza di collaborazioni internazionali che possono portare alla creazione di un network ampio per la richiesta di ulteriori fondi competitivi internazionali. Per la realizzazione delle attività previste sono messi a disposizione altri fondi, senza i quali il progetto sarebbe difficilmente sostenibile.

Sono state evidenziate le criticità che vengono qui di seguito riassunte.

Nel progetto non è presente alcun supporto grafico e manca un timeline che raffiguri sequenza, durata ed arco temporale di ogni singola attività del progetto. I deliverables non sono descritti in modo puntuale. I proponenti evidenziano alcune difficoltà a realizzare il progetto ma indicano parzialmente le modalità di gestione di tali rischi.

Project: DELIVERABLE MULTIVALENT METAL-BASED THERANOSTIC DRUGS

Applicant: Dolmella Alessandro

Giudizio Commissione Esterna**General assessment of scientific quality and innovation**

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*
- *Has the project the character of start-up research that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

Theranostics is an important area offering a transition between conventional cancer treatments and personalised medicine. Therefore, I appreciate that this project may have developmental prospects. But, its details and therefore the novelty expected of these applications, albeit outside my area of expertise, have not been explained clearly.

Reviewer n. 2

The project develops in the field of multitarget agents with potential application as theranostics. The absence of a specific strategy for specific targeting of tumor cells lowers the attractiveness of the project when looking for future competitive and non-competitive funds.

Reviewer n. 3

The leading concept of the proposal is to generate new therapeutic agents in which a linker conjugates a radioligand with tyrosine kinase inhibitor. The hypothesis is that such compound is expected to maximize the therapeutic efficacy of the individual ones. If successful this strategy could be extended to other compounds, paving the way to novel approaches which would attract funding and patents.

Reviewer n. 4

Targeting Tyrosine kinases by compounds combination (different linkers) of an organic-head (Kinase Inhibitors) and a metal-head delivered as encapsulated liposomes.

Original project, proof-of-concept with good possibilities of following up if successful and getting further competitive funds.

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Is the project supported by adequate human resources (young scientists, PhD students, etc.)?*

Reviewer n. 1

While the key aspects of the proposal are outside my area of expertise, the idea of liposomal delivery is not clear to me. What would determine the specificity of these liposomes to cancer cells?

There is no identified researcher to undertake this project.

Reviewer n. 2

The work plan is clear, but it is not clear why the applicant selected class III RTK inhibitors as a component of the new molecular objects. The medicinal chemistry part of the project (type of linkers and dithiocarbamates) has not been discussed. Deliverables could be affected by the lack of PhD or MSc students to carry out at least part of the synthetic work.

Reviewer n. 3

The work load of the proposed aims is demanding and, therefore, the applicant explicitly plans to compensate with adequate human resources from collaborating teams at UP and CNR.

<p>Reviewer n. 4 The abstract could have been a bit more clearly explained, also more detail to the biological part Task4 would have been of advantage. Four national collaborations, no PhD students mentioned.</p>
<p>Competence and expertise of the applicant.</p> <ul style="list-style-type: none"> - <i>What are the merits and scientific expertise of the applicant?</i> - <i>Are they appropriate and sufficient for the proposed project?</i>
<p>Reviewer n. 1 It is in the right area with regard to drug synthesis.</p> <p>Reviewer n. 2 The applicant has a long-standing experience in radiopharmaceuticals, an important asset for the project.</p> <p>Reviewer n. 3 The applicant has extensive international research experience and has gained expertise with diversified research approaches. Highly productive, the applicant has the adequate expertise to fulfil the planned goals.</p> <p>Reviewer n. 4 Publications supportive for the successful project development.</p>
<p>Competence and expertise of the research team.</p> <ul style="list-style-type: none"> - <i>Does the research team bring complementary expertise to the project?</i> - <i>Is the project involved in international research collaborations that can significantly contribute to the success of the project?</i>
<p>Reviewer n. 1 There is a strong team with somewhat overlapping but also complementary range of expertise. There is one external collaborator but no international partners.</p> <p>Reviewer n. 2 The team members bring complementary expertise for moving the project forward. No international collaborations are in place.</p> <p>Reviewer n. 3 The applicant plans an extensive network of highly qualified national and/or local collaborators. They are all important contributors of the planned research. No international collaborations are planned at this stage.</p> <p>Reviewer n. 4 Although collaborations outside of the department, no international ones. The national team is very solid.</p>
<p>Overall assessment</p> <ul style="list-style-type: none"> - <i>Strengths and Weaknesses</i>
<p>Reviewer n. 1 This project is outside my area of expertise but I am not convinced by the liposomal delivery. Furthermore, there is no clearly identified researcher to undertake this project.</p> <p>Reviewer n. 2 S – Strong and complementary expertise of team members. W - Lack of specific tumor cell targeting moiety in liposomes.</p> <p>Reviewer n. 3 Strengths: Totally innovative research subject that could be extended to other therapeutic agents. Potential to attract competitive funding and establish important collaborations with international teams. Weakness: The biggest concern relies on whether and to what extent the linkers compromise the efficacy of the drugs, by limiting their mobility and/or providing a spatial hindrance that may compromise with the binding to the receptor. One suggestion is to try to encapsulate the radioligand and the kinase inhibitor in liposomes without the linker and test whether a synergistic effect is equally achieved.</p> <p>Reviewer n. 4 Would have benefited from a bit more of explanation at some points of the application, for example which kind of tyrosine kinases are planned to be targeted by the developed compounds, or why several ratios of</p>

metal to organic heads will be trialed, and how the liposomes would be targeted to cancer cells in future in vivo experiments. This would make it easier for the reviewers.
The project would have benefited by the inclusion of a student.

Giudizio Commissione Interna

Il progetto si colloca nell'ambito della ricerca di trattamenti in campo oncologico, utilizzando competenze presenti sia nel DSF che in altri centri di ricerca. Il progetto è presentato in modo chiaro e la tematica è coerente con le linee di sviluppo del Dipartimento. I profili scientifici del proponente e del team sono di ottimo livello con una multidisciplinarietà di competenze previste dal progetto.

Sono state evidenziate le criticità che vengono qui di seguito riassunte.

Pur essendo presenti figure esplicative, sarebbe stato utile introdurre tabelle e diagrammi di flusso per una più efficace comprensione del testo.

Sebbene il PI abbia esperienza nelle tematiche proposte, non emerge in maniera chiara il suo personale contributo nei tasks previsti per lo svolgimento del progetto. Per quanto riguarda i componenti del team non è evidente l'expertise per la realizzazione di alcuni tasks.

L'analisi del rischio non è sufficientemente dettagliata e pertanto il contingency plan risulta incompleto.

Non è indicata la presenza di un partenariato (accademico e/o industriale) ampio per dare un respiro internazionale al progetto.

Project: NATURAL POLYPHENOLIC COMPOUNDS AND RELATED SYNTHETIC DERIVATIVES AGAINST ALPHA-GLUCOSIDASE AND PROTEIN GLYCATION TO OBTAIN NEW AGENTS FOR PERIPHERAL ARTERY DISEASE

Applicant: Frolidi Guglielmina

Giudizio Commissione Esterna

General assessment of scientific quality and innovation

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*
- *Has the project the character of start-up research that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

I have no doubts that natural products represent an important part in pharmaceuticals development. However, this is not explained clearly. Therefore, I am unable to comment on the future impact of this study.

Reviewer n. 2

The rationale of the project is not presented in a clear way. The choice of the natural compounds to be studied is not explained. The project could attract interest if the team found interesting molecules.

Reviewer n. 3

The project aims at exploring the role of plant derived polyphenolic compounds in inhibition of α -glucosidase, glycoxidation and AGEs production. The project includes the participation of several researchers favouring the establishing of collaborations. However, international collaborations are not foreseen.

If successful the study has the potential to launch start-up research on natural compounds to treat vascular damage occurring in numerous pathological conditions.

Reviewer n. 4

Investigation of five natural phenols and mangostin-related synthetic compounds by docking on α -glucosidase. In silico prediction of ADME Tox. Projection: vascular diseases and peripheral artery disease. Some glucosidase inhibitors are already approved and in development, however no derivatives from mangostin.

In silico ADME Tox will reduce the number of animal experimentation.

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Is the project supported by adequate human resources (young scientists, PhD students, etc.)?*

Reviewer n. 1

It is not clear whether the selected polyphenols are novel compounds, which will be isolated, or whether these are to be purchased. Some mangostin-based compounds might be synthesised via a collaboration but the origins of luteolin, rosmarinic acid, eupatorin are not stated clearly. Are the 3 tests to be performed for all these compounds? The time laps microscopy as a tool to study cellular ROS production may be helpful but is not quantitative enough for comparisons.

The personnel funding is only 12K – would it be sufficient for an appropriately qualified researcher? It seems that the work is expected to be done by project students. It is not realistic and certainly inefficient. Some co-financing is available.

Reviewer n. 2

The objectives are clearly presented; however, the rationale of the objectives is not explained in a clear way. In particular, no preliminary data or references supporting the use of the HUVEC assay as a good model of vascular damage are provided.

Reviewer n. 3

The aims of the project are clearly described as well as the strategies to reach them. However, the main hypothesis of the proposal is not clearly explained, e.g. why these plant derived polyphenolic compounds are expected to inhibit α -glucosidase, glycoxidation and AGEs production. A protective effect of these molecules on the vascular system is mentioned, but the necessary information on why these molecules are expected to impact the analysed pathways, thereby explaining the rationale behind the project, are not provided.

Reviewer n. 4

One young researcher is included in the funding.

It should have been clearly stated that xanthenes are alpha-glucosidase inhibitors at any point of the description. The reviewers had to look for additional information in this case.

Competence and expertise of the applicant.

- *What are the merits and scientific expertise of the applicant?*
- *Are they appropriate and sufficient for the proposed project?*

Reviewer n. 1

Extensive and appropriate for the proposed work.

Reviewer n. 2

The applicant has a background in natural compound pharmacological characterization.

Reviewer n. 3

The applicant's scientific profile is excellent and appropriate to address the topics proposed in the project.

Reviewer n. 4

The publication record of the applicant and expertise are supportive for the project. The missing in silico modelling part will be performed by a collaborator.

Competence and expertise of the research team.

- *Does the research team bring complementary expertise to the project?*
- *Is the project involved in international research collaborations that can significantly contribute to the success of the project?*

Reviewer n. 1

There is a good, complementary team. Collaboration with Genoa. No international partners.

Reviewer n. 2

The team members have complementary expertise. No international collaborations are in place or foreseen

Reviewer n. 3

The project relies on the undisputable expertise of the applicant and excellent and complementary research network. Important international collaborations seem not to be included.

Reviewer n. 4

National collaborators: in silico Dr. Tonelli, Genova. Co-PI, Coordination, statistics Prof. Ragazzi, Padova.

The co-PI has not included corresponding author publications.

Overall assessment

- *Strengths and Weaknesses*

Reviewer n. 1

Although this proposal is outside my area of expertise, I am not convinced that it is a well-designed one. There is lack of preliminary data on any of these compounds, the HUVEC as an only cell model is not perfect. There is no clear workforce assigned.

Reviewer n. 2

S – Expertise of the applicant on characterization of the pharmacological properties of natural products.

W – The rationale of the project is not compelling.

W – In vitro model of in vivo vascular damage not supported with preliminary data or references.

Reviewer n. 3**Weaknesses:**

The applicant does not plan to publish negative results, which is a great loss for the resources invested in the project: negative results are anyway results and, as such, need to be available to the scientific community.

The project scientific hypothesis is not clearly stated and, therefore, the rationale of the experiments is poorly enucleated. Without this information the prediction of the risk assessment on the project is not possible.

Strengths: If successful the project will identify novel compounds which could be considered for the treatment of vascular problems occurring in many diseases.

Reviewer n. 4

Although risks are summarized, no contingency plan is suggested.

Giudizio Commissione Interna

Il progetto è ben descritto e il razionale è interessante con possibili ricadute pratiche per la terapia di malattie vascolari associate al diabete. La tematica è coerente con le linee di sviluppo del Dipartimento.

I profili scientifici del proponente e dei componenti il team sono appropriati e coprono competenze farmacologiche e chimico-farmaceutiche adeguate alla realizzazione del progetto.

Sono state evidenziate le criticità che vengono qui di seguito riassunte.

Sebbene le molecole oggetto dello studio possano avere interessanti ricadute pratiche, il progetto non descrive chiaramente l'innovatività della ricerca e la strategia di design. Non sono indicati chiaramente i compiti del PI e del team e i dettagli relativi al razionale della sintesi e modeling dei nuovi composti.

Per una più efficace comprensione del testo sarebbe stato utile inserire diagrammi di flusso. La descrizione dei milestone e dei breakthrough è piuttosto generica e la risk analysis non è sufficientemente dettagliata.

Non emerge la presenza di un partenariato (accademico e/o industriale) ampio per dare un respiro internazionale al progetto.

Project: INVESTIGATION ON THE PHOTOSTABILITY OF CANNABINOIDS AND OF NOVEL PSYCHOACTIVE SUBSTANCES IN SEIZED PRODUCTS AND HAIR SAMPLES

Applicant: Miolo Giorgia

Giudizio Commissione Esterna**General assessment of scientific quality and innovation**

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*
- *Has the project the character of start-up research that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

This project sits outside my area of expertise. But I can imagine that its successful completion could help the department becoming a unique centre for this type of research, which could help attracting grants, business partners and research collaborations. However, I am not sure how original and innovative the proposal is, which would be paramount.

Reviewer n. 2

The project may give an important contribution to forensic analysis. The results could be of help in lawsuits and for ensuring that relevant specimens are properly stored for future use

Reviewer n. 3

The project is important for forensic toxicology. It will provide important information on the evaluation of drug intake by analysing hair samples. Any ground-breaking outcome of this project is difficult to be predicted.

Reviewer n. 4

Study of the photostability of cannabinoids (also synthetic) in hair samples (e.g. forensic studies) Photolysis studies of synthetic cannabinoids is novel. However, a preliminary experiment showing whether some of the compounds are photostable or not, would have been supportive to assure the success of the project.

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Is the project supported by adequate human resources (young scientists, PhD students, etc..)?*

Reviewer n. 1

The objectives are clear and appear easily achievable. My confidence would be higher if any preliminary data were available. The specific methodology seems to be fairly standard and well established in the applicants' labs.

All the work is apparently to be done by the team members. I am not sure how realistic this is. The funding component for the equipment is rather substantial but consists of non-specialised items. Is this necessary?

Reviewer n. 2

The objectives have been clearly presented and tasks properly assigned. Resources for materials are assigned properly. Accomplishment of activities appear to rely on senior researchers. Budget for young scientists could have been foreseen.

Reviewer n. 3

The overall goals of the project are described. However, the underlying scientific rationale is often omitted and left to the reader. The working hypotheses of individual tasks are not stated and it is therefore difficult

to assess the scientific impact of work packages. The methods are instead deeply described, although largely a copy and paste of published papers, e.g. Miolo et al, Brain Sci 2018.

Reviewer n. 4

Task 2: Preparation of samples and analysis of cannabis products by GC-MS months 6-12 seems a bit long.

No young researches involved.

Competence and expertise of the applicant.

- *What are the merits and scientific expertise of the applicant?*
- *Are they appropriate and sufficient for the proposed project?*

Reviewer n. 1

Very extensive and appropriate.

Reviewer n. 2

The applicant has a long-standing experience in the field. No issues are foreseen for the management of the project from a scientifically point of view.

Reviewer n. 3

The applicant is very well qualified to pursue the project.

Reviewer n. 4

The publication record and expertise of the applicant are fitting very well the objectives and plan of the project application.

Competence and expertise of the research team.

- *Does the research team bring complementary expertise to the project?*
- *Is the project involved in international research collaborations that can significantly contribute to the success of the project?*

Reviewer n. 1

The team is excellent, clearly covering all the required aspects of the project and involves an important international collaborator.

Reviewer n. 2

The team members bring complementary expertise needed to advance the project. An international research collaboration is in place.

Reviewer n. 3

All collaborations are highly qualified and complementary to reach the project's goals.

Reviewer n. 4

International: Task3: Prof Schifano (UK)

Supportive national partners: Task 4: Prof. Favretto, Padova. Task 2: Prof. Frison, Venezia.

Overall assessment

- *Strengths and Weaknesses*

Reviewer n. 1

Given that similar work has not been or is not being done elsewhere, this proposal appears to have originality that may give the department some uniqueness and competitive advantage.

Reviewer n. 2

S – Excellent expertise of the applicant

S – Good match of expertise among collaborators

W – Research activities appear to rely on the work of senior researchers. This may lead to delays in completing the project's activities.

Reviewer n. 3

Strengths: The findings obtained from this project will be very useful to forensic toxicology

Weakness: The innovative aspects and the scientific breakthrough of the future results are not sufficiently addressed

Reviewer n. 4

Comment to the starting material to be analysed: The hair samples containing Cannabinoids were already exposed to sun light in the test-persons during some time before being collected. Why the analysis is not

done dividing the hairs in segments depending on the time that they were sunlight pre-exposed (e.g. 1 cm equivalent to one month of growth). The tip, last centimetre of the hair, would have been exposed already five months to sunlight previous to in vitro experiments of photolysis, and therefore the degradation products might be different.

Risk analysis: “the identification and quantification of organic and synthetic cannabinoids to be analysed for this project could be under risk if the molecules under study are photostable, thus nothing happens to the samples upon irradiation”. Could it have not been a preliminary experiment for the project?

Giudizio Commissione Interna

Il progetto presentato è interessante e di rilevanza analitica in ambito forense e prevede un partenariato anche internazionale. È parzialmente in linea con la ricerca effettuata nel DSF.

I profili scientifici del proponente e dei componenti il team sono appropriati e adatti allo scopo della ricerca proposta. Il progetto è ben strutturato e sono indicati chiaramente i compiti di ogni unità coinvolta.

Sono state evidenziate le criticità che vengono qui di seguito riassunte.

Sebbene nel titolo si dichiara che il progetto mira allo studio della fotostabilità di cannabinoidi e di nuove sostanze psicoattive in prodotti sequestrati e in campioni di capello, dal testo emerge che lo studio si focalizza solo sulla valutazione di cannabinoidi di sintesi e naturali, per i quali peraltro il PI indica che sia già riportata in letteratura una riduzione del titolo dovuta ad esposizione alla luce.

La risk analysis non tiene conto della continua evoluzione del mercato delle sostanze psicoattive.

Per una più efficace comprensione del testo sarebbe stato utile ridurre la descrizione puntuale della procedura analitica prediligendo l'utilizzo di figure e diagrammi di flusso.

Il team prevede diverse e complementari competenze e la maggior parte del lavoro sembra sia previsto essere svolto in altri dipartimenti; non sono indicate in modo adeguato le possibili ricadute dei risultati attesi nel DSF.

Project: DEVELOPMENT OF NOVEL ANTI-HER2 TARGETED ANANAS FORMULATIONS FOR TREATING HER2+ BREAST CANCER

Applicant: Morpurgo Margherita

Giudizio Commissione Esterna

General assessment of scientific quality and innovation

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*
- *Has the project the character of start-up research that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

It is an innovative project on a very important aspect of cancer treatment and therefore health. Its successful completion would make a significant impact and open up opportunities for broad-spectrum collaborations and competitive grants. The proposal is anchored in the departmental know-how and technology developed by the applicants.

Reviewer n. 2

The project aims at expanding previous work carried out by the applicant at DSF to possibly extend the application of ANANAS nanoparticles. Project results could find application in therapy.

Reviewer n. 3

The outcome of this project has high potential for breast cancer treatment. If successful, this has the potential for patents, start-up and translational research. The applicant and her local network have already developed a ANANAS based delivery of active drugs to EGFR1 + triple negative breast cancer, obtaining outstanding results. Here they will verify whether the ANANAS strategy is a unifying successful drug delivery method. If successful this research will pave the way to highly useful therapeutic approach.

Reviewer n. 4

Investigation of ANANAS (avidin nucleic acid nanoassemblies)-based formulations for HE2+ breast tumors resistant to the antibody Trastuzumab with emtansine. To develop ANANAS-Cetuximab-emtansine. Previous: EGFR1-dependent vesicle-mediated internalization of cetux is more efficient when cetux is linked to ananas. Patents.

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Is the project supported by adequate human resources (young scientists, PhD students, etc.)?*

Reviewer n. 1

The scientific plan is described clearly and in details. The work packages are in line with deliverables and are achievable. Breast cancer lines work could be supported by analyses in primary cells to enhance clinical applicability. The MTT test is not sufficient for evaluating cell effects other than proliferation.

There is a logical progression between in vitro and in vivo experiments. Have the animal experiments been approved or are still under approval – this needs clarification. Otherwise, there is a clear contingency plan.

The personnel cost requested is realistic for one year and the need for further funding is acknowledged.

There is co-funding in collaborating labs making this proposal more economical.

Reviewer n. 2

The project plan is detailed. The applicant devised a very good risk and contingency plan. A significant risk for the project is the lack of funding for personnel for the second year.

<p>Reviewer n. 3 The hypothesis is clearly stated. The working plan is very well defined with clear and achievable milestones. The strategy of the research is established and therefore there is no concern on project feasibility.</p> <p>Reviewer n. 4 Two national collaborators (in vitro and in vivo parts). “Personnel” will be paid, but it is not described if a PhD student or a Postdoc fellow. Task 3.1- In vivo evaluation, month 17-24 seems a bit short. How many mice are estimated for the in vivo experiments?</p>
<p>Competence and expertise of the applicant.</p> <ul style="list-style-type: none"> - <i>What are the merits and scientific expertise of the applicant?</i> - <i>Are they appropriate and sufficient for the proposed project?</i>
<p>Reviewer n. 1 Excellent.</p> <p>Reviewer n. 2 The applicant has a strong publication record in the field. Her expertise will ensure a smooth progression of the research activities.</p> <p>Reviewer n. 3 The applicant has developed an outstanding research profile in applied nanomedicine. Her expertise is perfect for the success of this project.</p> <p>Reviewer n. 4 Very good track record and necessary technical expertise.</p>
<p>Competence and expertise of the research team.</p> <ul style="list-style-type: none"> - <i>Does the research team bring complementary expertise to the project?</i> - <i>Is the project involved in international research collaborations that can significantly contribute to the success of the project?</i>
<p>Reviewer n. 1 Very good, complementary, involving other institutions. No international partners yet.</p> <p>Reviewer n. 2 The two senior investigators that will collaborate to the project have complementary expertise with respect to the applicant. No international collaborations appear to be in place.</p> <p>Reviewer n. 3 The team planned for the realization of the project is composed of essential complementary expertise. International collaborations are not planned.</p> <p>Reviewer n. 4 Good complementary team.</p>
<p>Overall assessment</p> <ul style="list-style-type: none"> - <i>Strengths and Weaknesses</i>
<p>Reviewer n. 1 A very good, comprehensive proposal with a great developmental potential.</p> <p>Reviewer n. 2 S – strong expertise of the applicant S – complementary expertise of senior collaborators S – potential for generating new therapeutic agents W – funding for second year salary not secured: may threaten project completion</p> <p>Reviewer n. 3 Strengths: If the hypothesis will be proven valid, the results will bring high impact publication, high visibility for the institution and will introduce a treatment for forms of breast cancer which are currently resistant. Weakness: There is the risk that the ANANAS based strategy for treating HER2 positive breast cancer will</p>

result inefficient. Some preliminary data would be beneficial.

Reviewer n. 4

If there are already patients resistant to Trastuzumab-DM1 therapy as mention in the abstract, why they should not be resistant to Tz-DM1-ANANAS?

Formal: It would be helpful for the reviewers if the list of references at the end of the tasks would be completed with title etc. and the acronyms described “the first time” that they are mentioned and not afterwards.

Giudizio Commissione Interna

Il progetto si basa su un interessante razionale con una solida base di partenza considerando gli ottimi risultati preliminari. La tematica è coerente con le linee di sviluppo del Dipartimento.

Lo sviluppo della ricerca è ben strutturato con i ruoli e responsabilità dei diversi componenti del gruppo di ricerca facilmente identificabili, pur senza che siano stati evidenziati esplicitamente.

Risulta appropriato il profilo del PI, così come sono adeguati e complementari i profili scientifici dei partecipanti. Il team prevede la formazione di un consorzio con ricercatori di altri dipartimenti e altre Università, ed è adatto agli scopi prefissi.

La descrizione di milestone, breakthrough e risk analysis è molto precisa e corredata da figure e diagrammi esplicativi.

Per la realizzazione del progetto è previsto il contributo di altri finanziamenti per coprire le spese del team.

Sono state evidenziate le criticità che vengono qui di seguito riassunte.

Pur avendo il PI collaborazioni internazionali, non emerge il coinvolgimento di partner esteri per creare network più ampi finalizzati all’ideazione di progetti competitivi internazionali.

Project: TARGETING CCK2R FOR THE DELIVERY OF RADIOPHARMACEUTICALS IN THE TREATMENT OF SOLID TUMORS

Applicant: Realdon Nicola

Giudizio Commissione Esterna**General assessment of scientific quality and innovation**

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*
- *Has the project the character of start-up research that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

This is a very interesting project aimed at overcoming the drawbacks of antibody-driven radionuclide delivery and exploiting properties of a new radionuclide. It is well-anchored in departmental expertise, has collaborative links and should attract future funding and broad-spectrum collaborations.

Reviewer n. 2

The project aims at expanding application of an existing technology in order to obtain compounds for application as theranostics. It is built on department know-how and existing collaborations. The prospect for international collaborations and for attracting funds is high.

Reviewer n. 3

The outcome of this project has a very high potential for developing an innovative treatment to treat cancer using targeted radioligand therapy. It is innovative and builds on already proven potential of the ¹¹¹Ag in radiotherapy and selective expression of the CCK2R expression by cancer cells. Thus the project is relatively at low risk with a very high output potential. The development of such molecule will also be highly valuable for theranostics.

Reviewer n. 4

CCK2R targeting with radiopharmaceuticals in solid tumors. (Z-360 antagonist plus Ag(I)). Synthesis of Ag¹¹¹ chelating agents. High expression in tumors, low in healthy cells.
Very good project in the development of therapeutic radionuclides.

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Is the project supported by adequate human resources (young scientists, PhD students, etc.)?*

Reviewer n. 1

The objectives are clear and plan of work well explained, even for the non-specialist. The clear milestones are included. The plan involves complex synthesis and formulation steps but the applicant is well aware of this and has a fall back plan. The team is conversant in the methodology required and some preliminary data is available. Funding for an identified post-doc has been included.
N.B It is A549 cell.

Reviewer n. 2

Project's objectives and hypotheses are well described. The research plan is sound. The applicant conducted a thorough risk analysis and devised a contingency plan. Resources appear adequate.

Reviewer n. 3

The research hypothesis is very clearly stated and solid, building on published evidences and existing

<p>expertise in the laboratory and in the network. The workflow is realistically delineated, with excellent potential for optimal handling of technical and human resources. The risk plan is also concrete and adequately addressed.</p> <p>Reviewer n. 4 A postdoc fellow will be paid by the project with assigned tasks1. A PhD student in Task2.</p>
<p>Competence and expertise of the applicant.</p> <ul style="list-style-type: none"> - <i>What are the merits and scientific expertise of the applicant?</i> - <i>Are they appropriate and sufficient for the proposed project?</i>
<p>Reviewer n. 1 Excellent and very appropriate</p> <p>Reviewer n. 2 The scientific expertise of the applicant is absolutely fitting for the leadership of the project.</p> <p>Reviewer n. 3 The scientific expertise of the applicant is excellent and in line with the proposed project. Therefore, the project has high potential to be successfully delivered on time.</p> <p>Reviewer n. 4 Good track record and the necessary expertise for the project.</p>
<p>Competence and expertise of the research team.</p> <ul style="list-style-type: none"> - <i>Does the research team bring complementary expertise to the project?</i> - <i>Is the project involved in international research collaborations that can significantly contribute to the success of the project?</i>
<p>Reviewer n. 1 Very good. Includes the appropriate mixture of expertise and included both experienced and junior staff. However, no external or international collaborators but some potential has already been identified.</p> <p>Reviewer n. 2 The team members bring the complementary expertise needed to advance the project. No international collaborations are in place, but positive results could help establish such collaborations.</p> <p>Reviewer n. 3 Fundamental international collaborations are not clearly stated.</p> <p>Reviewer n. 4 The collaborators are national, but there are international collaborations planned.</p>
<p>Overall assessment</p> <ul style="list-style-type: none"> - <i>Strengths and Weaknesses</i>
<p>Reviewer n. 1 An innovative proposal with a significant potential to attract further funding and collaborations.</p> <p>Reviewer n. 2 S – The topic of the project has already a scientific validation. S – Strong expertise in the field of the applicant. W – The project might have contemplated a preliminary study of biodistribution of one of the delivery system in a xenograft tumor model.</p> <p>Reviewer n. 3 Weaknesses: The project largely relies on two synthesis at the beginning of the project. In case of failure delay and large delay of this task, the entire project will suffer a delay in delivering results. Strengths: The project is highly innovative, with high potential for additional funding and start-up and builds on solid established competences and strategies.</p> <p>Reviewer n. 4 Ref 25: in relation to Z-360 ligand... “a slight loss of affinity with no effect on specificity when CRL is conjugated to its payload via hydrophilic linkers”. How sure is it that the voluminous linker plus chelator do</p>

no influence targeting the receptor with Z-360?
Is there a reason why they do not buy Z-360 from companies (5mg, 100 EU), maybe it would save money/time invested in the synthesis?
How will it be in vivo when the natural ligand cholecystokinin-8 competes with the drug for the receptor?
Maybe affinity studies with SPR (DDS1 and yholecystokinin-8).

Giudizio Commissione Interna

Il progetto mira alla messa a punto di un sistema di drug delivery per la veicolazione di radionuclidi in cellule tumorali a scopo radioterapeutico. Il progetto è chiaro e strutturato bene e la tematica è coerente con le linee di sviluppo del DSF.

Il profilo del PI risulta appropriato, adeguati e complementari i profili scientifici dei partecipanti appartenenti anche ad altri dipartimenti e centri di ricerca.

Nel progetto è presente un ottimo supporto grafico sebbene non sia riportato un grafico timeline per definire la tempistica di realizzazione. I proponenti evidenziano una serie di rischi per la realizzazione del progetto ma anche individuano le strategie per superarli.

Data la complessità del progetto e la richiesta di una borsa di studio, in assenza di altri contributi, il progetto sembra difficilmente sostenibile: tuttavia il PI cita la presenza di collaborazioni internazionali che possono portare alla creazione di un network ampio per la richiesta di ulteriori fondi competitivi.

Sono state evidenziate le criticità che vengono qui di seguito riassunte.

La responsabilità dello svolgimento dei diversi tasks non è stata chiaramente indicata (solo da una breve nota nei CV del team) e per il PI non emerge il suo personale contributo nello svolgimento dell'attività scientifica prevista dal progetto.

Project: INTERACTION BETWEEN INTERMEDIATE FILAMENT PROTEINS AND G-RICH ONCOGENE PROMOTERS: A NOVEL PERSPECTIVE TO CONTROL GENE EXPRESSION

Applicant: Sissi Claudia

Giudizio Commissione Esterna

General assessment of scientific quality and innovation

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*
- *Has the project the character of start-up research that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

This proposal is based on the extensive expertise of the applicant. It is a very interesting basic research project but with the future application potential. It deals with the very current and important topic of gene expression related to chromatin organisation and the role of protein interactions in this process. Successful completion of this work would result in high quality publications and lead to grant applications and collaborations.

Reviewer n. 2

The project aims at shedding light on the interaction of vimentin with DNA. Results could trigger drug discovery projects in the oncology fields. The project builds on know-how available at the DSF. If successful, international collaborations could be established and competitive and non-competitive funds attracted.

Reviewer n. 3

The project aims at exploring the potential of vimentin in regulation of gene expression upon interaction with guanine rich regions of promoters. If proven valid, the hypothesis will identify a novel unifying mechanism to control gene expression and this will have important impact on basic science. Furthermore, it will provide important information on vimentin and vimentin-guanine rich regions interactions as potential target for novel therapeutics.

Reviewer n. 4

Interaction of intermediate filament proteins, Vimentin (Lamin B1 and other nuclear proteins), with oncogene (c-Kit) promoter regions (pull down, HDX-MS etc). Relevant: Interactions, potential pharmacological targets in cancer. Studies could extend to other pathologies with mis-regulation of cell-cycle is linked to IF proteins overexpression.

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Is the project supported by adequate human resources (young scientists, PhD students, etc..)?*

Reviewer n. 1

The objectives are clearly presented, the experimental plan is comprehensive and the 5 tasks are ambitious but appear achievable given that the methodology is established in the applicant's lab. There is some preliminary data but there is none showing the indicated sequence homology between vimentin and lamin B1. This would help supporting Task 5.

The team consists of two members and no specified researchers to perform the experiments has been identified or requested. Is it realistic for this small team to undertake all the planned experiments in a timely

<p>fashion?</p> <p>Reviewer n. 2 Activities to be conducted are clearly defined. The project appears to rely only on the work of the applicant and a collaborator. This may negatively affect the deliverables at the indicated time-points.</p> <p>Reviewer n. 3 The project network builds on the team of the applicant and another PI in the university of Padua. No further details on the composition of the team in terms of human resources are provided. Given the limited number of teams 2 and no indication on their composition, the adequate availability of human resources to reach the project goals is difficult to assess.</p> <p>Reviewer n. 4 It would have been helpful to know during the task-description that Vimentin and lamin B1 will be commercially acquired. This point is not described until the Risk analysis and contingency plan. PhD paid by another grant.</p>
<p>Competence and expertise of the applicant.</p> <ul style="list-style-type: none"> - <i>What are the merits and scientific expertise of the applicant?</i> - <i>Are they appropriate and sufficient for the proposed project?</i>
<p>Reviewer n. 1 Excellent and very relevant with several recent high quality publications in the subject area.</p> <p>Reviewer n. 2 The applicant has extensive experience in the field. Therefore, no issues can be reasonably foreseen for the advancement of the project.</p> <p>Reviewer n. 3 The applicant's expertise is adequate for the success of the project.</p> <p>Reviewer n. 4 Excellent publication record and experience related to the topic.</p>
<p>Competence and expertise of the research team.</p> <ul style="list-style-type: none"> - <i>Does the research team bring complementary expertise to the project?</i> - <i>Is the project involved in international research collaborations that can significantly contribute to the success of the project?</i>
<p>Reviewer n. 1 The team is very small and does not involve any specified researchers to perform the experiments. No collaborators.</p> <p>Reviewer n. 2 The team member brings the expertise in Mass Spectrometry that will be very important for the progression of the project.</p> <p>Reviewer n. 3 No international collaborations are planned. The applicant relies on internal expertise and collaborations are sufficient to deliver the milestone of the project.</p> <p>Reviewer n. 4 Padova collaborator Dr. Spolaore. Although standing international collaborations, not directly involved in the project.</p>
<p>Overall assessment</p> <ul style="list-style-type: none"> - <i>Strengths and Weaknesses</i>
<p>Reviewer n. 1 This proposal is anchored in the extensive expertise of the applicant but this has not been exploited to engage in broader collaborations and the human resources appear insufficient. These may hamper the work.</p> <p>Reviewer n. 2 S – Strong expertise in the field of the applicant.</p>

S – Many different techniques considered for carrying out the project's tasks.

W – Resources dedicated to the project may not ensure a sufficiently fast progression towards deliverables.

Reviewer n. 3

Weaknesses: Task 1 states that the project's preliminary results will be confirmed. This statement implies that the applicant's preliminary results on which the whole project builds seem not to be that solid. If the preliminary results are not confirmed, then the entire project risks to have very limited deliverable.

Strengths: The project has high potential to identify a novel molecular mechanism as target for innovative therapeutics.

Reviewer n. 4

Relevant topic and project. Very well organised tasks. Multiple methodological approaches.

It is not clear which tasks will be done by the PhD student. Neither if she will spend sometime abroad, and if it will be her only project or part of another one, in order to know if the time-lines are feasible.

Giudizio Commissione Interna

Il progetto è interessante e innovativo nelle sue ambizioni. Il team è interno al DSF e si propone di utilizzare nuove tecniche analitiche acquisite nel DSF. La tematica è coerente con le linee di sviluppo del Dipartimento.

I proponenti evidenziano una serie di rischi per la realizzazione del progetto ma anche individuano strategie alternative che però potrebbero ridurre parte dei risultati attesi.

Il team appare numericamente esiguo per poter realizzare un progetto così complesso; tuttavia, il PI ha collaborazioni internazionali che è auspicabile possano partecipare attivamente al progetto.

Sono state evidenziate le criticità che vengono qui di seguito riassunte.

La presentazione del progetto è molto specifica e tecnica, complicandone la lettura e comprensione.

Manca un adeguato supporto grafico accompagnato da diagrammi timeline esplicativi.

La responsabilità della ricerca dei vari tasks non è chiaramente descritta.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO JUNIOR PRID-J – ANNO 2019**Project: NEURO-COAGULOPATHY: ROLE OF BLOOD COAGULATION FACTOR XIIIa IN NEURODEGENERATION****Applicant:** Acquasaliente Laura**Giudizio Commissione Esterna****General assessment of scientific quality and innovation**

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*
- *Has the project the character of start-up research that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

This project is aimed at understanding mechanisms of cerebral amyloid angiopathy. As neurodegenerative diseases are a growing problem, this work is timely and, if completed successfully, likely to attract further funding and collaborations. It is built on some departmental know how but is speculative.

Reviewer n. 2

The project aims at addressing complex mechanisms by which proteins interact to form amyloid deposits. The project may add knowledge to this topic, as FXIIIa has been described to interact with A β . Most references are 15 to 20 years old. No international collaboration is in place.

Reviewer n. 3

The project aims at demonstrating the existence of a complex A β , NAC and FXIIIa that underlies the cerebral amyloid angiopathy. The hypothesis is solid and innovative. If proven valid, this regulatory system could be a target for novel therapeutics, thereby scoring a high impact for translational research. This research will also have a significant impact for basic science as it will uncover a previously unnoticed mechanism for amyloid fibrils formation. The project has the potential to attract competitive funding and highly qualified collaborations.

Reviewer n. 4

Identifying mechanisms of aggregation through the study of the interaction of (non amyloid b-component) NACs of aSyn to fibrinogen by FXIIIa crosslinking in cerebral amyloid angiopathy (CAA), prospectively finding new drugs which disrupt the interaction.

Good project with potential of development of new drugs.

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Is the project supported by adequate human resources (young scientists, PhD students, etc.)?*

Reviewer n. 1

The hypothesis is based on published studies and is logical. The methods are established and the experimental plan is acceptable. However, no preliminary data for the putative interactions are available. This makes the project very risky. Unfortunately, the risk analysis and contingency plan is focussed solely on the technical aspects and does not consider the lack of these putative interactions. No funding for a dedicated researcher has been requested – is the idea of PRID-J that all work is to be done by the applicant? See below RE: Team.

Reviewer n. 2

The project is expected to evolve through a number of steps, which have been well described from the technical point of view. The milestones and the expected results, however, appear too general. The allocation of resources is not convincing; the budget allocated for personnel is surprisingly low. The risk analysis and the contingency plan have not been addressed properly.

Reviewer n. 3

The main scientific hypothesis of the project as well as working hypothesis of each individual task is very well presented. The concepts are clearly expressed and fully justified by previous findings. The proposed research team is composed of several PIs with their research groups. Thus, human resources seem to be adequate to the development of the project.

Reviewer n. 4

Task 2: crosslinking of fibrinogen and plasma to NACs and aSyn by WB... can be challenging many products of different sizes? Smear? Plan B is MS, will it be better?

Task3: the same problem, SPR for a 1:1 reaction good, for oligomerization? PlanB, Isothermal titration calorimetry.

If a similar study with other oligomerizing proteins has been conducted, a Ref to show feasibility would have been good.

One graduate student included in budget.

Competence and expertise of the applicant.

- *What are the **merits and scientific expertise of the applicant?***
- *Are they **appropriate and sufficient for the proposed project?***

Reviewer n. 1

The applicant is a very competent and accomplished young scientist with all the expertise required for this project.

Reviewer n. 2

The applicant has the scientific expertise to bring the project forward.

Reviewer n. 3

The applicant has gained a number of experiences in several national and international laboratories. She will be perfectly able to be the supervisor of this research. She should develop a certain degree of independence from her early career advisers.

Reviewer n. 4

Several publications in the field, familiar with most of the techniques that will be necessary. Several stages abroad, however first time funding.

Competence and expertise of the research team.

- *Does the **research team bring complementary expertise to the project?***
- *Is the **project involved in international research collaborations that can significantly contribute to the success of the project?***

Reviewer n. 1

The team is very good, with a mixture of experienced and junior (post-doc) researchers and clinicians but the specific involvement of team members is not given. No external or international collaborations.

Reviewer n. 2

The competences and the expertise of the team members are adequate to support project's activities.

Reviewer n. 3

The proposed network of local and national collaborators is important for the success of the project. No important international collaborations are planned at this stage of the project. Increasing the project based collaborations would be beneficial to the competitiveness of the applicant.

Reviewer n. 4

No international collaborations foreseen. Mentioned but not described.

Overall assessment

- ***Strengths and Weaknesses***

Reviewer n. 1

It is a project in an important area based on an interesting hypothesis and submitted by a competent young researcher. But without any preliminary data it is risky. Perhaps a small amount of funding could be released to generate some preliminary binding data?

Reviewer n. 2

S – Appropriate expertise of the applicant and the team members.

S - Access to instrumentation allowing full characterization of protein-protein interactions

W – Translational value of the project to be verified, considering that various factors could be implicated in disease aetiology.

Reviewer n. 3

Strengths: Innovative, high impact for translational and basic research.

Weakness: The finding that A β , NAC and FXIIIa form a macromolecular regulatory complex in vitro does not imply the existence of in vivo. If possible, the existence of such putative complex should be confirmed in biological brain samples.

Reviewer n. 4

Challenging project, outstanding if successful with projections in drug discovery.

Clearly written even for non-specialists in the topic.

(-) Comment to the proposal: I noticed in the abstract a paragraph very similar to another paragraph written in an application that has been withdrawn.

Giudizio Commissione Interna

Il progetto presentato si basa su un buon rationale e un solido background, ed in accordo con le linee di ricerca sviluppate nel DSF. Il rationale ed il work package sono chiari e ben descritti in tutte le componenti, tali da giustificare la fattibilità.

Risulta interessante l'utilizzo sinergico di tecniche analitiche presenti nel DSF, come pure l'applicazione di strumentazione acquisita recentemente.

Il team è adeguato al progetto e appaiono interessanti le sinergie con ricercatori di altri Dipartimenti della Scuola di Medicina dell'Università di Padova.

Sono state evidenziate le criticità che vengono qui di seguito riassunte.

Il progetto non è supportato da adeguato materiale grafico.

Il team è coerente con lo scopo della ricerca ma non viene ben specificato il ruolo di ciascun partecipante. Sebbene siano evidenziati chiaramente alcuni possibili rischi, il contingency plan non è appropriato.

Project: EXTRACELLULAR VESICLES AS DELIVERY CARRIERS OF ONCOLYTIC VIRUSES AND THERAPEUTIC AGENTS FOR THE TREATMENT OF MESOTHELIOMA

Applicant: Garofalo Mariangela

Giudizio Commissione Esterna

General assessment of scientific quality and innovation

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*
- *Has the project the character of start-up research that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

Mesothelioma is a hard to treat cancer but it is rare and its prevalence in Italy is not particularly high. While I understand the need to work on neglected diseases, the proposal does not explain the fundamental link between the treatment modality and this particular tumour. However, the idea is interesting, exploits own recent data and has a potential to attract future funding and collaborations.

Reviewer n. 2

The project aims at an innovative approach for the treatment of cancer. It takes advantage of a network of international collaborators, and can attract competitive and non-competitive funds. Of note, a patent application has been filed.

Reviewer n. 3

This project aims at encapsulating the newly engineered oncolytic adenovirus vectors As5D2a-ICOSL plus other anti-neoplastic formulations in mesothelioma cell line derived extracellular vesicles (EV) and test the efficacy of the virus-EV, drugs-EV and virus-drugs-EV in vitro on different cell lines. In vivo testing in animals is planned in future studies, when the in vitro mechanisms will be fully characterized. The project is highly innovative and the potential output could greatly impact the treatment of mesothelioma and could potentially be extended to other cancers.

The project exploits a number of established and novel highly established international collaborators. As presented, the work flow does not indicate clearly the extent of work performed locally and what tasks are up to the international collaborators and why.

Reviewer n. 4

Delivery of therapeutic oncolytic virus and therapeutic agents with extracellular vesicles (EV) as a therapy for asbestos-induced cancer for which there is no directed therapy except standard chemotherapy. Why the PI wants to express ICOSL is not clear (oncolytic adenovirus vector Ad5D24-ICOSL).

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Is the project supported by adequate human resources (young scientists, PhD students, etc.)?*

Reviewer n. 1

The hypothesis linking the oncolytic virus and EV containing chemotherapeutic agents is not explained well. In contrast, the methods and work packages have been described in minute details.

The risks and contingency plan for methodological aspects have been well thought out but the general principle of EV actions have not. No research personnel applied for. Is the PRID-J designed that all work is to be done by the applicant?

Reviewer n. 2

The project plan is clearly described and appears to be feasible. It seems that most of the activities will be carried out by the applicant. It is not clear whether the activities performed in collaboration with experts abroad will be performed by post-docs/technicians in the experts' labs.

Reviewer n. 3

The methods of all aims are clearly described in detail, including the experimental conditions. The rationale of research is clear for AIM2 and 3, but a bit unclear for AIM 1.

The time requested for each task in all aims is indicated by the applicant. However, the local human resources employed on this project are not listed. Therefore, the prediction of feasibility of each individual task within the proposed time line is hard to determine.

The driving hypothesis of the research proposal is unclear. Is the main focus establishing the therapeutic efficacy of the adenovirus (Ad5D24-ICOSL) engineered by the applicant or its efficacy upon EV-based delivery or both? It is not clear to me whether the therapeutic capacity of the Ad5D24-ICOSL is already established. If not, then the success of AIM2 and AIM3 is highly dependent on AIM1. If yes, then the goal of AIM1 is a bit undefined to me, but AIM2 and 3 would be certainly of high value.

Reviewer n. 4

-AIM1, characterization of adenovirus is not clear. Mesothelioma cell lines will be infected to express ICOSL....why, to activate T-cells? Explanation would have been of advantage for non-T-cell researchers. "WT control (construct without ICOSL)", means simply "mock" or "empty" adenovirus backbone? WT is in this case not adequate, or there is also a mutant?

-AIM2. EVs "according to in house protocol". Two short sentences explanatory of how the extracellular vesicles are formed would be of advantage.

-No PhD students involved.

Competence and expertise of the applicant.

- *What are the merits and scientific expertise of the applicant?*
- *Are they appropriate and sufficient for the proposed project?*

Reviewer n. 1

Very appropriate expertise and excellent track record.

Reviewer n. 2

The applicant has the scientific background and the expertise to bring the project forward.

Reviewer n. 3

The applicant has invested in several national and international experiences and worked in different laboratories, progressively increasing her expertise and building knowledge in drug delivery. Her scientific production is interesting and reveals an adequate degree of independence from early career supervisors. This independence is also mirrored by the obtained grants to fund her post-doctoral activities. Her expertise is perfect for the proposed project.

Reviewer n. 4

The PI has demonstrated that she can get funding, has an appropriate publication output and expertise in the topic.

Competence and expertise of the research team.

- *Does the research team bring complementary expertise to the project?*
- *Is the project involved in international research collaborations that can significantly contribute to the success of the project?*

Reviewer n. 1

The team is excellent, highly complementary and international. It is a great example of exploiting established contacts to strengthen grant applications.

Reviewer n. 2

The research team features scientists with different type of expertise, who can ensure a strong support to the project.

Reviewer n. 3

World class experts are involved in this project. They are mainly established collaborators of the applicant and the project is therefore expected to progress fluently.

Reviewer n. 4

Four international collaborators.

Overall assessment

- *Strengths and Weaknesses*

Reviewer n. 1

I wish the hypothesis was explained better because it is an interesting proposal by a competent and accomplished young scientist who managed to assemble a formidable team of international collaborators. I hope that the applicant will find the time required to do the extensive experimental work.

Reviewer n. 2

S – The approach is innovative allowing cutting edge research.

S – Strong scientific background of the applicant and the team members.

S – Potential for translational research: a patent application has been filed.

W – It appears that some activities will be carried out outside DSF: this might negatively affect timelines.

Reviewer n. 3

Strengths: The project has the potential of highly impact the treatment for mesothelioma. The involved research network is highly qualified and proven to work productively with the applicant. All procedures are planned in detailed as well as a risk analysis and contingency plan.

Weakness: Research hypothesis could be expressed more clearly and straightforward.

Reviewer n. 4

Very interesting project with very good possibilities for publication and patenting, but it could have been more clearly written in a way that the reviewers do not need to look for additional information.

(-) it would have been helpful to briefly introduce how the adenovirus will work, if it is T-cell activation how is it that in AIM1 they are using other cancer cell lines?

Formal comment: Abstract, State of the Art and Aim of the work, are a bit repetitive.

Giudizio Commissione Interna

Il progetto presentato è innovativo e fondato su un solido background. Pur non facendo parte delle classiche linee di ricerca sviluppate nel DSF, si avvale di competenze nel campo del delivery presenti nel dipartimento e di metodiche/campi di applicazione potenzialmente sviluppabili grazie al progetto stesso.

Il PI ha già una buona esperienza nel settore. Il team è adeguato al progetto sia per numerosità che per background scientifico. L'interesse della tematica coinvolge da subito un qualificato team internazionale presupposto per ulteriori future collaborazioni. Risulta molto interessante l'acquisizione di nuove competenze e temi di ricerca per il Dipartimento e la possibilità di instaurare collaborazioni internazionali con ricercatori in Austria, Finlandia e Svizzera.

La risk analysis è ben definita.

Sono state evidenziate le criticità che vengono qui di seguito riassunte.

Il progetto non è supportato da materiale grafico adeguato.

Emerge il problema della gestione logistica di un team suddiviso in più sedi, vista l'entità del finanziamento e la possibilità di lavorare con virus, attività che richiede un laboratorio opportunamente attrezzato ed autorizzato.

Project: NEW CHEMICAL PROBES FOR RNA: STUDY OF RNA STRUCTURE BY MASS SPECTROMETRY-BASED APPROACH**Applicant:** Susic Alice**Giudizio Commissione Esterna****General assessment of scientific quality and innovation**

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*
- *Has the project the character of start-up research that can attract in the future competitive and non-competitive funds?*

Reviewer n. 1

The RNA toxicity, interactions and exploitation of inhibitory RNAs as a treatment modality are all very topical. Moreover, the project exploits applicant's discovery in this area. Therefore, the project has a chance to create impact, attract further funding and extend the already good collaborators' base. Successful completion may indeed help establishing the Department as a centre of excellence in this area.

Reviewer n. 2

The project takes advantage of the knowledge available at DSF on a class of probe and on the expertise the applicant has acquired. There is already a network in place to help advance the project.

Reviewer n. 3

This research proposal aims at developing methods to study the RNA and RNA complexes based on a recently newly designed class of nucleic acids (Bis-3-chloropiperidines). The final goal is establishing an advanced spectrometry-based RNA analytical platform. Given the importance of developing such methods in terms of collaboration and future applications for start-ups and participations to advanced research networks, the innovative scientific concept of this research project is unclear to me.

Reviewer n. 4

Development of new RNA chemical probes (Bis-3-chloropiperidines; B-CePS library, RNA crosslinker). MS-based platform for RNA. Open to new international collaborations.

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*
- *Is the project supported by adequate human resources (young scientists, PhD students, etc.)?*

Reviewer n. 1

The project is unfocussed. It consists of two elements, both that could suffice for an entire project. Otherwise, the objectives and plans are described in a very detailed and clear way and are logical. Given the experience of the applicant and the collaborative arrangements in place, the plan might be realistic albeit it is ambitious.

There is a named PhD student identified to perform this work. Would it be during the entire project? I like the ambitious aspiration to organise an international conference in Padova.

Reviewer n. 2

Two objectives of the project are described in the Aim of Work. Activities in the Work Packages, however, do not seem to address the first objective (s. page 2). It is not clear why one of the tasks is focused on building a nano-ESI in house: is there no commercial set up available? It is also not clear how much will the

<p>PhD and other students at DSF contribute to the project.</p> <p>Reviewer n. 3 While the project largely builds on the consolidated expertise of the applicant and her research networks, it is unclear the amount of the local human resources destined to pursuing the research. Probably there is an imbalance between the available human resources and the ambitious goals of the project.</p> <p>Reviewer n. 4 How difficult is Task2A “In-house building of the nano electrospray setup”? Controls missing (i.e. for crosslinking, how good are the new crosslinkers?). Which is the rationale behind task 3B? HeLa cells treated with the crosslinker and isolation of the MALAT1-RNA to map the B-CePS binding sites. Will not all the RNA in the cell be crosslinked? Selectivity of the crosslinker? What is the PhD student going to do exactly?</p>
<p>Competence and expertise of the applicant.</p> <ul style="list-style-type: none"> - <i>What are the merits and scientific expertise of the applicant?</i> - <i>Are they appropriate and sufficient for the proposed project?</i>
<p>Reviewer n. 1 Excellent and very much in the area.</p> <p>Reviewer n. 2 The applicant has the necessary scientific expertise to lead the project.</p> <p>Reviewer n. 3 The applicant has an international profile and has been the recipient of competitive research grants. She has built competence and a valuable international network.</p> <p>Reviewer n. 4 Appropriate experience, CV and publication record.</p>
<p>Competence and expertise of the research team.</p> <ul style="list-style-type: none"> - <i>Does the research team bring complementary expertise to the project?</i> - <i>Is the project involved in international research collaborations that can significantly contribute to the success of the project?</i>
<p>Reviewer n. 1 There is a named PhD student on this project and 3 international collaborators who bring specific expertise and contribution to the project.</p> <p>Reviewer n. 2 The research team may take advantage of collaborations with PIs abroad, who have specific expertise and can provide inputs and guidance on specific topics that will be addressed in the project.</p> <p>Reviewer n. 3 The project relies on the expertise of the applicant and her local collaboration. Furthermore, a strong international network of highly qualified scientists is involved in the development of the proposed research.</p> <p>Reviewer n. 4 Three good international collaborations with experts in the topic.</p>
<p>Overall assessment</p> <ul style="list-style-type: none"> - <i>Strengths and Weaknesses</i>
<p>Reviewer n. 1 It is an ambitious albeit a bit unfocused project by a young but accomplished PI, who managed to assemble a great international team of collaborators. Its successful completion may lead to the establishment of the department as a centre of excellence.</p> <p>Reviewer n. 2 S – Expertise and network of collaborators of the applicant. W – Misalignment between Work Packages and Objectives as reported in the Aim of the Work.</p> <p>Reviewer n. 3 Strengths: Very timely research topic addressed with state of the art techniques. The establishment of the</p>

mass-spectrometry based platform in studying RNA and RNA in complexes could be highly beneficial for the department in terms of collaborations with external scientists. However, the risk that this platform shifts to a facility service has to be considered and avoided.

Weakness: The degree of independence of the applicant from her early career supervisors is to be proven.

Reviewer n. 4

(+) Novelty in the department and beneficial for collaborations. But there is not foreseen how other groups can benefit from it.

(+) Important topic in drug development.

(-) The project relies on Task 2A “building of the nano electrospray setup”. If this part is not achieved the project will not develop.

(-) Selectivity of the crosslinkers in cells experiments.

(-) Controls of each task are missing. For example they could be some of the small-molecules included in the Revision by Warner et al that the PI included in the application.

Giudizio Commissione Interna

Il progetto è interessante, ben scritto e chiaramente articolato e rientra nelle linee di ricerca sviluppate nel DSF. Risulta corredato da uno strutturato supporto grafico che schematizza chiaramente le tappe previste per la realizzazione.

Il PI ha già una buona esperienza nel settore. Il team è adeguato ed internazionale ed è anche previsto l’apporto di un giovane dottorando. Questo progetto mira a creare un network multidisciplinare e internazionale per poter competere in progetti europei.

Sono chiari alcuni possibili rischi nella realizzazione del progetto ma sono evidenziate le strategie per superarli.

Sono state evidenziate le criticità che vengono qui di seguito riassunte.

Emerge il problema della gestione logistica di un team suddiviso in più sedi vista anche l’entità del finanziamento.

VALUTAZIONI ASSEGNI DI RICERCA DI DIPARTIMENTO DI TIPO B ARD-B – ANNO 2019

Project: POLYMERIC SYSTEM FOR MANUFACTURING ANTICANCER VACCINES DIRECTED TO ANTIGEN PRESENTING CELLS

Applicant: Bellato Federica

Giudizio Commissione Esterna

General assessment of scientific quality and innovation

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*

Reviewer n. 1

This project exploits the existing idea but gives it a novel twist. The successful completion would make a significant contribution to the field. Based on the existing departmental expertise, it is also developmental and should attract collaborations and further funding.

Reviewer n. 2

The project can be regarded as an “incremental innovation” approach to cancer vaccines.

It is built on a sound department know-how, and holds the potential for future applicative development and international collaborations.

Reviewer n. 3

The research proposed in this plan is timely and proposes the development of an anti-tumor vaccination. The obtained results will be instrumental to follow-up grant proposal application and has the potential to introduce an important turning point in the field.

Reviewer n. 4

Very good project on the design of polymer-nuclei acid systems which target APC by binding the Mannose receptor, for anticancer vaccination.

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*

Reviewer n. 1

The hypothesis is sound, objectives described clearly. The project is ambitious as only some of the polymer libraries are available. There is a fair bit of fine-tuning required. The use of RNA has a clear advantage for targeting but RNA stability is lower than DNA. It might be fine for short RNAs but integrity of mRNA required for expression might be problematic. However, importantly, this problem has been recognised and addressed albeit gel analysis may not be sufficient to evaluate whether RNA could be translated effectively. Task 3 is ambitious but well designed.

Reviewer n. 2

Activities are presented in a clear way.

Reviewer n. 3

The hypothesis is clearly presented. The research plan is realistic and feasible and relies on the expertise of the applicant and that provided by the collaborators.

Reviewer n. 4

Safety and biocompatibility: why not also using human blood besides rat blood?

Also CHO are hamster cells and JAWSII mice, why not human dendritic cells?

<p>Competence and expertise of the applicant.</p> <ul style="list-style-type: none"> - <i>What are the merits and scientific expertise of the applicant?</i> - <i>Are they appropriate and sufficient for the proposed project?</i>
<p>Reviewer n. 1</p> <p>The applicant is still a PhD student. She has some relevant expertise, including a period of studies at a collaborating lab in the project area. She has no first author papers yet but her work was noticed and awarded at an AAPS conference.</p> <p>Would the applicant be the PI and not just the post-doctoral researcher on this project?</p> <p>Reviewer n. 2</p> <p>The applicant has previous experience in the field, which is expected to ensure a smooth progression of activities.</p> <p>Reviewer n. 3</p> <p>The applicant has developed a wide range of research strategy in anti-cancer compounds and drug delivery tools and has also adequate experience with cell biology techniques. Altogether, this expertise is fundamental to pursue the presented project.</p> <p>Reviewer n. 4</p> <p>3 publications, however no first authorship.</p>
<p>Competence and expertise of the supervisor and of the research team.</p> <ul style="list-style-type: none"> - <i>Does the research team bring complementary expertise to the project?</i> - <i>Is the project involved in international research collaborations that can significantly contribute to the success of the project?</i>
<p>Reviewer n. 1</p> <p>This is an accomplished team with complementary expertise. This is a great advantage providing that the applicant would not be reduced to the post-doc role.</p> <p>Reviewer n. 2</p> <p>The supervisor and the team have the expertise to fully support the research activities.</p> <p>Reviewer n. 3</p> <p>The planned network of collaboration brings complementary expertise to the project.</p> <p>Reviewer n. 4</p> <p>Very good research team. International collaboration with Prof. Cerullo, Univ. Helsinki.</p>
<p>Overall assessment</p> <ul style="list-style-type: none"> - <i>Strengths and Weaknesses</i>
<p>Reviewer n. 1</p> <p>It appears that the applicant will be the main (only) researcher on this project. It would be important that she is also leading it as the true PI. There is no information on the amount required for this project (clarification here would be helpful) but there is 12K co-financing available.</p> <p>Reviewer n. 2</p> <p>S - Potential for translational application of the outcomes; S - Team with strong and complementary expertise in the field; W – The contingency plan does not include a back-up strategy</p> <p>Reviewer n. 3</p> <p>Strengths: The planned research is innovative and has the potential to be attractive for other grants, establish novel international collaborations, consolidate the existing ones and pave the basis for the future career of the applicant as independent PI.</p> <p>Weaknesses: Planning a stay-abroad at this stage in world class laboratories on the topic of research would be greatly beneficial for the applicant and her career development.</p> <p>Reviewer n. 4</p> <p>Project based on previous solid work, what is reassuring for its success. Some mobility during the project, abroad stay would benefit the project.</p>

Giudizio Commissione Interna

Il progetto presentato si basa su un buon razionale ed un solido background, e rientra nelle linee di ricerca sviluppate nel DSF. Il razionale ed il work package sono chiari e ben descritti in tutte le componenti, così da rendere lo sviluppo del progetto comprensibile e attuabile.

Il team è adeguato al progetto.

Dal CV e dalle pubblicazioni presentate si evince la presenza di competenze adeguate per la realizzazione del progetto.

Project: ROLE OF ESTROGENS AND GENDER IN THE FUNCTIONAL REGULATION OF GLYCOLYTIC PROTEINS IN HUMAN ENDOTHELIAL CELLS: IMPLICATIONS FOR NOVEL THERAPEUTIC APPROACHES

Applicant: Boscaro Carlotta

Giudizio Commissione Esterna

General assessment of scientific quality and innovation

- *Is the project scientifically significant, original and innovative?*
- *Is the project built on a departmental know-how?*
- *Has the project a significant impact for future development?*
- *This project has perspective for international collaborations, applications, networking?*

Reviewer n. 1

The project is very interesting and innovative being based on new findings, also from this lab. It is original and has a great potential for impact and broad spectrum medical but also cross-disciplinary collaborations. It is based on the departmental expertise.

Reviewer n. 2

The project has the potential to further expand the knowledge on the effect of miRNAs in angiogenesis and its involvement in cancer.

Reviewer n. 3

This research project is in the frontline of contemporary research and exploits the miRNA dependent regulation to explain differences of receptor expression observed in pathologic condition. The applicant is highly ambitious and aims at improving her professional profile in order to be competitive at international level. This line of research, moving from the expertise of her PhD supervisor and now including miRNA regulation of protein expression, may represent the field in which her future career as independent PI will develop.

Reviewer n. 4

miRNAs identification in GLUT1/PFKFB3 pathways and effects in angiogenesis. Effect of GPER agonists in miRNAs. Aim, to develop miRNA-based therapeutics with the desired estrogen effects or blocking the pathological function and definition of sex specific miRNAs. Future in vivo studies open the door to interdisciplinary collaborations.

Assessment of scientific plan

- *Are the objectives and hypotheses clearly presented?*
- *Is the plan realistically feasible?*
- *Are the research methods, materials, work packages and timeline appropriate and in agreement with deliverables?*

Reviewer n. 1

The objectives and hypothesis are clearly presented. However, the experiments have been described for the expert in this area and so I find it difficult to evaluate the feasibility fully. The availability of one of the luciferase reporter vectors will greatly facilitate the work progress. However, this will provide a readout only. How are the miRNAs be identified? This is one of the deliverables and leads to 2.1 (miRNA overexpression testing). Otherwise, the experimental approach is consistent with the aims and based on the departmental expertise.

Reviewer n. 2

Overall, the project is well presented. The experimental part is very detailed. The deliverable, however, appear challenging considering that most of the work will have to be performed by the applicant only.

Reviewer n. 3

The hypothesis is clearly stated, built on published evidences and pervious results of the applicant and the research team in which she is involved.

The applicant has exhaustively designed the experiments to address her hypothesis.

Reviewer n. 4

Some of the parts were not too clear for an outsider of the topic.

Competence and expertise of the applicant.

- *What are the merits and scientific expertise of the applicant?*
- *Are they appropriate and sufficient for the proposed project?*

Reviewer n. 1

The applicant is still a PhD student. She has relevant expertise, as the proposed study is a continuation of her PhD project. She has no first author papers yet but co-authored 4 publications, two of these in the area of study.

Would the applicant be the PI and not just the post-doctoral researcher on this project?

Reviewer n. 2

It seems that the applicant does not have a previous experience in miRNAs. The willingness to embark in this challenging project is remarkable.

Reviewer n. 3

The project builds in part on the applicant's expertise. However, the scientific hypothesis builds also on miRNA, which is not the major expertise of the applicant and her direct supervisor. Major advice will be provided by a local collaborator.

Reviewer n. 4

The missing experience will be complemented by the aid of the collaborators.

The proponent has four publications although none as first author.

Competence and expertise of the supervisor and of the research team.

- *Does the research team bring complementary expertise to the project?*
- *Is the project involved in international research collaborations that can significantly contribute to the success of the project?*

Reviewer n. 1

This is an accomplished research/supervisory team with a range of complementary expertise. This is a great advantage providing that the applicant would not be just a post-doc.

Reviewer n. 2

It seems that a solid background and competence in the miRNA field is not present in the team.

Reviewer n. 3

The planned network of collaboration brings complementary expertise to the project. International research collaborations are not planned.

Reviewer n. 4

Collaborators: Prof Mitro, Milan, Prof. Sandona, Padova. Dr. Carotti, Padova.

Overall assessment

- *Strengths and Weaknesses*

Reviewer n. 1

I might have missed it but I cannot see the miRNA identification step in this proposal. Not being able to evaluate it, I find it difficult to comment on the subsequent steps.

It appears that the applicant will be the main (only) researcher on this project and it would be important that she is also leading it. I am not clear on the funding required for this project. Clarification here would be helpful as it is not a cheap project.

Reviewer n. 2

S – The team has a good expertise in the biology of endothelial cells.

W – It not clear whether enough experience is available on miRNA biology.

Reviewer n. 3

Strengths: State of the art research strategy based on the latest advances of the revolutionary role of non-coding RNA. Great potential to initiate the career of the applicant as principal investigator.

Weaknesses: Planning a stay-abroad at this stage in world class laboratories on miRNA research would be greatly beneficial for the applicant and the project.

Reviewer n. 4

Mobility during the project development would be beneficial.

Giudizio Commissione Interna

Il progetto presentato è innovativo, fondato su un solido background, e descritto in modo molto chiaro e preciso in tutte le componenti.

Risulta molto interessante l'acquisizione per l'assegnista di nuove competenze in collaborazione con il dipartimento di Scienze Biomediche.

Il team è adeguato al progetto sia per numerosità che per background scientifico.

Dal CV e dalle pubblicazioni presentate si evince la presenza delle competenze necessarie per la realizzazione del progetto.