VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2024

COMMISSIONE ESTERNA

Project: Do novel dual COX-2 inhibitors/TP receptor antagonists regulate the immune response in the tumor inflammatory microenvironment?
Applicant: Bolego Chiara

General assessment of scientific quality and innovation - Assessment of scientific plan

- *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? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate** and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives 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 background is exhaustively described and the goals are clearly presented. The project is scientifically meaningful, although originality and innovativity are somehow limited, given the studies already performed by the research group. The planned activities, relying on departmental know-how, are feasible and the results may have a significant impact for future development. The work packages are sufficiently well organized and described, the proposed timelines appear appropriate and the deliverables sound, although not precisely indicated. The risk analysis is maybe tackled and solved too quickly. The research team appears appropriate and components seem to have complementary expertise.

Reviewer n. 2

The project is scientifically significant and concerns an interesting area of investigation with a still high medical need. The planned activities are based on a good group's know-how, the project originates from some interesting preliminary results, and proposed timelines appear appropriate. The risk analysis is appropriate as well as the research network. On the other hands, the profile of the selected chemical tools is questionable for what concerns the selectivity, and I wonder whether other tools have been considered as well as the use of combinations of more selective and not double acting compounds. Also, it is not clearly explained whether the benign safety profile of the tool compounds has been experimentally proven or is just hypothesised.

Reviewer n. 3

The project is scientifically significant and will give us new responses regarding the crosstalk between inflammation and immune response in TME in the wake of numerous articles reporting the role of COX2 and tumor immune response. The project relies on departmental know-how and exploit complementary expertise of other groups of research showing its multidisciplinary nature. The project shows a significant impact for future development to better understand the mechanistic role of immuno inflammation in tumor growth and in developing of new pharmacological therapies. The plan is challenging but given the PI's and collaborators' experience, it is feasible and I retain the project description in line with deliverables. The major part of the experiments is carried on in agreement with the laboratories know-how, possible problems could be overcome. However, PI does not take into consideration possible problems that could be encountered during the project not directly linked to her lab but related to the activities of the other lab in collaboration. The project has perspectives for international collaborations and networking as already reported regarding Dr. Zinato at the School of Biochemistry and Immunology at Trinity College in Dublin under the supervision of Prof. Luke O'Neill and regarding Prof Sala's project on eicosanoids. The project could highlight the potentiality of the COX-2 inhibitor/TP antagonists as anticancer. These properties, if confirmed, could represent a basis to attract competitive and non-competitive funds. Moreover, also the

immune-regulatory role of eicosanoids in cancer could attract interest. Furthermore, the project results will strengthen the networking activity leading to future grant application consortia.

Reviewer n. 4

This is a multidisciplinary project, which involve a team of scientists with a potential high impact. The project represents a strong base for further grant applications.

The knowledge obtained in the development of the project will allow for the identification of novel combination therapies for cancer research. The project includes 3 work packages, with a strong collaboration with all the team members and collaborators. The methodologies, expected results, and contingency plans are well described.

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 PI has a strong background and expertise for the project, apparently fully adequate to carry on the project.

Reviewer n. 2

The applicant has most of the required competence and expertise to support the project. She should however consider the chemical side relevant in the selection of tool compounds.

Reviewer n. 3

The PI has a strong background in investigating the pathophysiological role and pharmacological modulation of endothelial cells, innate immune cells, including human monocyte and macrophage immunophenotypes, and platelet function, all knowledge of relevance for the project. Moreover, PI has numerous collaborations in order to fulfil some gaps of the research thanks to the complementary activities of the other labs. At the moment the competences and expertise of the PI seems to be sufficient in order to carry on the project and to approach some concerns with the other labs in collaboration.

Reviewer n. 4

The PI has a documented publication record proving her expertise in immune pharmacology. There is no doubt that she can lead the project and manage the collaborations.

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 research team shows complementary activities, suitable to cover the various areas of research regarding the project.

Reviewer n. 2

The team expresses most of the complementary expertise required by the project and a good integration of competences in different research groups. However, a medicinal chemistry competence is missing, and it would help the potential evaluation and selection of different chemical tools to get the project objectives.

Reviewer n. 3

The research team shows complementary activities in order to fill different areas of research regarding the project. At the moment, the project provides collaborations with italian groups but with the potentiality to expand, given the collaboration of the PhD student Maddalena Zinato involved in the project, at the School of Biochemistry and Immunology at Trinity College in Dublin with a fellowship under the supervision of Prof. Luke O'Neill. This will foster a potential collaboration with Prof. O'Neill's group.

Reviewer n. 4

The team is strong and multidisciplinary, including oncologists and pharmacologists. Nevertheless, the team lacks international collaborators.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2024

COMMISSIONE INTERNA

Project: Do novel dual COX-2 inhibitors/TP receptor antagonists regulate the immune response in the tumor inflammatory microenvironment?
Applicant: Bolego Chiara

Punti di forza
Il progetto risulta interessante poiché propone di esplorare il ruolo degli inibitori selettivi della COX-2 e degli antagonisti del recettore TP nella risposta immunitaria e nell'infiammazione all'interno del microambiente tumorale pro-infiammatorio.

Criticità
Non è chiaro quale sia la patologia target che il progetto intende affrontare; in alcuni punti si fa riferimento al cancro al seno, mentre in altri si menziona il cancro al colon, senza fornire una spiegazione al riguardo. Inoltre, la fenotipizzazione delle cellule T dovrebbe essere implementata anche utilizzando campioni di pazienti. Qualora questi non fossero disponibili, sarebbe opportuno includere questo aspetto nell'analisi dei rischi.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2024

COMMISSIONE ESTERNA

Project: Senescent cells and their secretory phenotype as targets for aging related-diseases therapy
Applicant: Montopoli Monica

General assessment of scientific quality and innovation - Assessment of scientific plan

- *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? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate** and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives 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 originality of the project is low, given that its main aim is to continue the screening, already started some years ago, of the anti-senescence activity of natural and synthetic compounds through in vitro assays. The project is built only partially on departmental know-how, since it is not clear whether the expertise for the in vivo assays is adequate. The methods, materials and work packages are very hastily described and the timeline is missing. The collaboration with professor Alimonti could give strength to the proposal but it is not clear whether he is part of the research team, since his CV is not present. The risk assessment is quite modest and the possibility to attract competitive and non-competitive funds is moderate.

Reviewer n. 2

The project is not well described, and several key information are missing both in the abstract and in the body of the proposal. The objectives are not clearly described (as an example, it is not clear whether they want to consider natural and synthetic compounds or just natural extracts). The risk analysis is not complete, and it should be revised. While the described activities are all feasible in an overall timespan of two years, the individual WPs are not clearly presented in terms of timelines and responsibilities. Also, the proponent does not specify her time commitment. The whole proposal does not encompass any medicinal chemistry activity, which should instead be considered throughout the project, particularly in the case the initial hits fail to provide positive results (risk analysis). Finally, in the introductory part there is not any reference to potential competition, or other groups' activities.

Reviewer n. 3

The research project has the merit to focalise in study of new natural composts useful to counteract ageing, strongly involved in several diseases in addition to having a relevant impact on the aging populations. The plan is realistically feasible, given the departmental know-how. Indeed, the involved groups have a strong background in performing these analyses as also demonstrated by the previous research on Salvia haenkei. The project is well reported and milestones and timeline are appropriated for the deliverables. The group of research involved in the project have strong experience on the proposed analyses. However, WP3 is reported to be carried on by Professor Alimonti's lab of IOR (Bellinzona) but he is not reported in the group of research and it is not reported the cv. Principal risk factors are reported and possible solutions are proposed but there are no considerations for possible risk factors in WP3. The project has the potential for networking and could have the character of start-up research in order to produce new senolytic active pharmaceuticals useful in the aged population and in age-related disorders.

Reviewer n. 4

Anti-aging therapy is an interesting strategy to improve healthcare and quality of life. Nevertheless, this project is lacking several details, making it difficult to follow and evaluate the potential impact of the research. It is not clear how the project will develop, the techniques used, the experiments proposed, therefore it is impossible to assess feasibility in the 2 years of the project.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2024

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 Only limited indication of the competence and expertise of the applicant can be drawn from the proposal **Reviewer n. 2** The applicant's competence and expertise are sufficient to support some of the proposed activities, but in view of the drug discovery nature of the project, she has not the required minimal competence in this area. **Reviewer n. 3** The applicant has adequate competence for the analyses and procedures required in the project as already demonstrated with the research on Salvia haenkei extract. This project proposes again the same procedure of selection of relevant natural compounds with senolytic properties. **Reviewer n. 4** The PI has the expertise to lead the project. Her publication record confirms her expertise in characterizing natural compounds with pharmacological activity.
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 Professor Alimonti, who is in charge for WP3, is not included in the research team. **Reviewer n. 2** The team does not bring the required complementary expertise required by the project. Also, it is not clear the effective team's composition (are Proff Alimonti e Dall'Acqua effective team members?). **Reviewer n. 3** The research team is characterized by the same competence. The proposal reports that WP3 will be carried out in collaboration with Prof. Alimonti's lab of IOR (Bellinzona) that it is not inserted into the list of the research team. Therefore, this information is misleading. Prof Alimonti is not reported as a member of the team but in the proposal are reported his publications. **Reviewer n. 4** The research team is formed by the PI and two early stages researchers, in charge of the experimental work. Also, no international collaborations are listed.

COMMISSIONE INTERNA

Project: Senescent cells and their secretory phenotype as targets for aging related-diseases therapy
Applicant: Montopoli Monica
Punti di forza
Il progetto ha l'obiettivo di identificare molecole in grado di interferire con i processi di senescenza cellulare al fine di mitigare i processi di invecchiamento.

Criticità
Il progetto si propone di selezionare composti con attività senolitica attraverso sperimentazione in vitro e poi di testare i composti in vivo nel topo. Tuttavia, per quanto riguarda gli esperimenti in vitro non risulta chiaro il criterio di scelta delle differenti linee cellulari. La sperimentazione in vivo prevede lo studio della farmacocinetica dei composti selezionati ma non sono resi noti i criteri per la selezione, i dosaggi, la modalità di trattamento in vivo. Inoltre non è fatto alcun riferimento all'autorizzazione alla sperimentazione animale quindi non è chiaro se è stata presentata e in attesa di approvazione o se già approvata. Ci sono delle discrepanze in merito ai componenti del team e non è definito il loro ruolo.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2024

COMMISSIONE ESTERNA

Project: EngineerINg systems To countERact inFluEnza viRal infEctions (INTERFERE)
Applicant: Morpurgo Margherita

General assessment of scientific quality and innovation - Assessment of scientific plan

- *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? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate** and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives 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 project, thoroughly developed and punctually described, is built on departmental know-how and the plan is realistically feasible. The methods and work packages are briefly but very precisely outlined, tasks and milestones are fully detailed. The risk assessment is sound. The possibility of networking is solid and the ability to attract funds is certain.

Reviewer n. 2

The project is very interesting and innovative; it can provide important new weapon against viral infections. The proposal is well written, even though miss clear reference to potential competition. Also, the proposed timelines seem a bit overestimated. The necessary know-how is fully in place as well as the materials and methodologies; the preliminary results obtained with SARS-CoV-2 form a very good basis for the proposed activities. One key point is missing in the risk analysis, that is what if the behaviour of the new constructs results different from what obtained in the preliminary activity, eg either a different correlation with the receptor density or not correlation at all. At the moment, there are no collaboration with external or industrial research group, which could strongly support the project in case of positive results.

Reviewer n. 3

Research is scientifically significant, original and innovative. Results of previous similar research demonstrated that viral receptor multimerization using a non-lipid bilayer nanocore permitted obtaining semisynthetic nanodecoys with similar potency as those based on lipid bilayer vesicles, with the advantage of much simpler and reproducible optimization and preparation processes. The project is ambitious with the aim to optimize nanodecoys capable of efficiently inhibiting influenza virus infectivity using a nanoplatform characterized by high fidelity, reproducibility and rapid scalability. Moreover, it could be applicable to a number of viral infections formulating a broad-spectrum approach to prevent infection of different influenza subtypes. The project was built with the departmental know-how with up to date instrumentations. The project has a significant impact for the future development and the plan is realistically feasible. The project is well written and tasks are in line with the proposed milestones.

The applicant considers properly possible risks and applied a contingency plan. Moreover, the project has perspectives for collaborations and networking and part of the project is already realized in the Academic Spin off ANANAS nanotech S.r.l. (2007).

Reviewer n. 4

This project in based on expertise of the Department, with a strong team of collaborators, and can have a strong impact. The proposal can be easily implemented for further grant applications. The rationale, the workflow and all the aspects of the project are well described, including a solid contingency plan. The ANANAS Nanoconstructs are well established material, potentially diminishing the novelty of this proposal, but making it a strong starting basis for novel application in the treatment of viral infections.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID – ANNO 2024

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 has the scientific expertise to fully manage and coordinate the proposed project. **Reviewer n. 2** The applicant has specific competence and know-how concerning the proposed activities; her background and experience span almost all the research areas involved with the project **Reviewer n. 3** The applicant has expertise in planning and supervising the optimization of ANANAS/SA/NAI assemblies, their physico-chemical characterization and the affinity studies. This expertise is appropriate for the proposed project. Moreover, the project will involve other participants with strong and complementary abilities to complete the project with a well-structured supervision. **Reviewer n. 4** The PI has several publications in high impact factor journals on the development of ANANAS. There is no doubt that she can lead the research team and that she has the expertise for the successful completion of the project.
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 research team is wide and well-structured, bringing together complementary expertise. **Reviewer n. 2** The research team is well balanced with all the required proficiencies involved. It maybe that an external collaboration from industrial setting could help the future development in case of initial positive results. **Reviewer n. 3** The research team comprises investigators with diverse and complementary expertise ranging from pharmaco-technology, medicinal chemistry and virology. At the moment the project involve only groups of the University of Padova. The research group shows complementary and strong expertise for developing and concluding the project. The project has the potentiality to be expanded to international collaborations. **Reviewer n. 4** The PI has several publications in high impact factor journals on the development of ANANAS. There is no doubt that she can lead the research team and that she has the expertise for the successful completion of the project.

COMMISSIONE INTERNA

Project: EngineerINg systems To countERact inFluEnza viRal infEctions (INTERFERE)
Applicant: Morpurgo Margherita
Punti di forza
Il progetto si propone di sviluppare e ottimizzare una piattaforma in grado di utilizzare specifiche nanoparticelle, con l'intento di integrare i metodi terapeutici e preventivi tradizionali contro le infezioni virali. Il progetto é altamente innovativo in quanto intende rispondere all'urgente necessità di misure efficaci per la prevenzione e il controllo delle infezioni.

Criticità
Nonostante la proponente si proponga di supervisionare l'intero progetto, buona parte di esso (WP3-Task 3.1 e WP4) sarà svolta presso il Dipartimento di Medicina Molecolare.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2024

COMMISSIONE ESTERNA

Project: Impairing Importin α5-Mediated Nrf2 Nuclear Translocation as a Novel Strategy for Treating Chemoresistant Medulloblastoma
Applicant: Bortolozzi Roberta

General assessment of scientific quality and innovation - Assessment of scientific plan

- *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? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate** and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives 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 project is scientifically significant and original. It is built on departmental know-how and the plan appears feasible, although ambitious. The methods, materials, work packages and tasks appear appropriate and sufficiently described. The risk assessment and contingency plan are missing. Possible international collaborations and networking are not taken explicitly into consideration.

Reviewer n. 2
The project aims to target Nrf2 pathway to treat medulloblastoma. The medical need is high, as there is no efficacious treatment of this tumor, which often presents recurrence. Nrf2 is an interesting target, albeit difficult to reach. The project is well described, and the workload is reasonable to be completed in 2 years. Nevertheless, there is not a backup plan, if any step is not successfully completed. The research team is multidisciplinary and well-aligned with the expertise of the department.

Reviewer n. 3
The project concerns an area of high medical need, it is scientifically significant, and relatively original and innovative. In case of positive results, it may have a strong impact on future activities in the same area. According to the summary and the WPs, I found it a bit complicated to evaluate the effective feasibility of the whole project and to estimate the proposed timelines. While a key objective of the project is indeed the discovery and characterization of new lead compounds, the flow of activities and foreseen timelines are more focused on the establishment of new biological methods and tools; I found indeed extremely difficult to consider just couple of months as refinement period of initial leads; also the computational and synthetic know-how resides out of the department and this may complicate the relative work and timelines. Also, the risk assessment has been considered only in part, while it is clearly a high-risk project. In essence, I found the project very interesting and worth of consideration, but it should be globally revised and, at least, written in a better format (and including figs).

Reviewer n. 4
The project is scientifically significant considering the role of Nrf2 in the onset and maintenance of chemotherapy resistance in medulloblastoma and other cancer types, this project aims to identify new compounds able to prevent Nrf2 transcriptional activity and improve the effects of chemotherapy.
Part of the project evaluates the ability of the new inhibitor to penetrate the tumoroid mass, it will be important also evaluate its ability to pass the BBB by the collaboration with the Department of Industrial Engineering of the University of Padova. Methods, materials, work packages, tasks, milestones and timeline are appropriated and in agreement with deliverables.
Another risk may be due to the low inhibitory activity of the tested compound and also the difficulty of the compound for the penetration in 3D cultures. Applicant does not report a contingency plan for these issues.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2024

The project already exploits international collaboration for compound production to be tested and it could have character for start-up research.

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 has the scientific expertise to supervise and carry on the project.

Reviewer n. 2

The PI has a strong record of publications, on the development of pharmacological approaches for cancer therapy. The expertise of the PI is in line with what presented in the proposal, and she can lead and coordinate the research team.

Reviewer n. 3

The proponent has a great experience for what concerns the biological side of the project, well covering the relative activities. At the same time, she does not have apparently experience for what concerns the initial part of the project, that is the medicinal chemistry side, one of the key areas.

Reviewer n. 4

Applicant has expertise in the identification of new targets and therapeutic strategies in childhood acute lymphoblastic leukemia and medulloblastoma, with a particular focus on the study of the mechanisms of drug resistance, development of in vitro models of chemotherapy resistance, study of metabolic alterations in cancer and screening and biological evaluation of newly synthesized anti-tumoral compounds. Applicant has strong experience to supervise all phases of the project.
The scientific expertise is appropriate and sufficient for the proposed project.

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 research team is adequate to cover complementary expertise.

Reviewer n. 2

The project involves an international team with complementary expertise, including a chemist for the synthesis of the inhibitors of Nrf2 and an expert in brain and pediatric tumors.

Reviewer n. 3

The team bring a good complementarity and internationality to the project, but it is not clear how and if the computational and chemistry activities are effectively part of the project (see the WPs).

Reviewer n. 4

The research team has strong expertise to approach all tasks and the project is involved in international collaborations with Prof. Matteo Borgini (Augusta University, GA, USA) for the synthesis of the inhibitory peptides in WP1.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2024

COMMISSIONE INTERNA

Project: Impairing Importin α5-Mediated Nrf2 Nuclear Translocation as a Novel Strategy for Treating Chemoresistant Medulloblastoma

Applicant: Roberta Bortolozzi

Punti di forza

ll progetto, concentrandosi sull'identificazione di inibitori selettivi di Nrf2, è altamente innovativo e affronta un problema clinico importante con metodologie avanzate e un approccio razionale. Il progetto è scritto in modo chiaro e comprensibile, presentando obiettivi ben definiti.

Criticità

Data la complessità del target Nrf2 e le sfide tecniche inerenti ai modelli utilizzati, sarebbe stato opportuno includere un'analisi dei rischi approfondita, che purtroppo è assente. Inoltre, il ruolo dei diversi partecipanti al progetto non è delineato in modo chiaro.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2024

COMMISSIONE ESTERNA

Project: A proteomic approach to study the dysregulation of proteolytic activity and oxidative state in Inflammatory Bowel Diseases
Applicant: Franchin Cinzia

General assessment of scientific quality and innovation - Assessment of scientific plan

- *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? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate** and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives 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 proposal, exhaustively described, is original and significant. The plan is really wide and quite ambitious. The methods, materials and work packages are consistent with the deliverables and the risk assessment is punctually and critically performed. The project has the possibility to foster international collaborations and opens the way to develop a start-up.

Reviewer n. 2
This proposal describes a proteomic approach to identify molecular mechanisms in Inflammatory Bowel Diseases. The project is well written, describe clearly deliverable and milestones. The risk analysis and contingency plan for each task is a great strength of this proposal. The timeline is clear and allows adequate time to data analysis. The results obtained can be translated to other pathologies, and therefore the findings can be a good starting point for grant applications.

Reviewer n. 3
A very well written proposal, scientifically significant and based on a pool of solid information. The departmental know-how is good concerning both the methods and the technologies required, as well documented. The innovation potential seems to reside on the optimization of existing methods, while I do not see a great originality in the proposed approach. The risk assessment is appropriate and well described; from this point of view I wonder whether a further risk does exist, that is the existence of correlation between the markers of just a group of diseases instead of with all (providing this has a sense).
According to the proposed plans, I wonder why the collection of blood samples are not included within the tasks (neither the relative researcher) and whether the given planned commitment of the two team members are enough in view of the given timelines.

Reviewer n. 4
The project is scientifically significant, original and innovative given its trying to quantify oxidized vWF that normally required excessively large starting blood volumes (200 ml). Results of the project could be helpful to extrapolate other unconventional processes related to the initiation of coagulation cascade (oxidative stress and microbial infection) correlated not only with IBD but also with several diseases that present a higher risk of developing thrombosis: Type-2 Diabetes, Chronic Kidney Disease, Rheumatoid Arthritis, COVID-19, and sepsis.
The optimizations produced in task 1 could be applied for the study of other pathologies where these steps are required, becoming a powerful tool for future applications.
The project has a significant impact for future development also for the study of other pathologies reporting problems in blood coagulation. The project takes into consideration the departmental know-how and its development will help to acquire new know-how for LC-MS/MS technology. The project is challenging but

could be realistically feasible. Risk assessment is well reported with a relative and appropriate contingency plan for each considered task.
Results obtained by the project could be helpful for activating international collaboration and also useful to initiate collaboration with biotechnological companies as commercial partners. Results of the project could permit the development of a diagnostic and prognostic essay, involving a biotechnological company as commercial partner.

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 technical expertise of the applicant is richly described and adequate for the development of the project, although some doubts about its feasibility could ensue, given the multiplicity of tasks that need to be carried out.
Reviewer n. 2
The PI has a proven scientific production on protein biology, including proteomics, protein characterization and protein chemistry. She has the expertise to lead this project.
Reviewer n. 3
Applicant's competence and experience are good enough to most of the proposed activities but would need probably some help for data management.
Reviewer n. 4
The applicant has strong expertise in proteomics, in particular in LC-MS/MS techniques applied to untargeted and targeted research. Merits and expertise are perfectly in line with the proposed project.

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 research team is based only on a PhD student, clearly not enough to fulfil all the tasks indicated in the project.
Reviewer n. 2
The team is insufficient to fulfil the requirements of the project. Only a doctoral student with low commitment is indicated, no national nor international partners. Therefore, it is unclear how the project will be developed.
Reviewer n. 3
The second team member has a similar competence as the applicant, with lower experience. Further know-how could be usefully brought by others, like an expert in chemo- and bioinformatics.
Reviewer n. 4
The team is composed by only 2 people with complementary expertise in order to cover all the project analyses. Indeed, hematological analyses will be carried out by Dr Cavedon with experience in this field. At the moment the project is not involved in international collaborations.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2024

COMMISSIONE INTERNA

Project: A proteomic approach to study the dysregulation of proteolytic activity and oxidative state in Inflammatory Bowel Diseases

Applicant: Cinzia Franchin

Punti di forza

L'utilizzo delle tecniche proteomiche per indagare il legame tra IBD e attivazione non convenzionale della cascata coagulativa rappresenta un approccio scientificamente avanzato e potenzialmente innovativo. La tematica proposta è nuova ma il background del PI è pienamente adeguato allo sviluppo del progetto.

Criticità

Seppur scritto in modo comprensibile, il progetto non sempre risulta di facile lettura a causa di alcune parti (task e milestone) ripetute nelle diverse sezioni del progetto.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2024

COMMISSIONE ESTERNA

Project: Development of multicellular 3D in vitro models of metabolic dysfunction-associated steatohepatitis for the advanced screening of active natural compounds and extracts
Applicant: Gabbia Daniela

General assessment of scientific quality and innovation - Assessment of scientific plan

- *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? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate** and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives 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 project is significant and original. The plan appears realistically feasible, although very challenging. Methods, materials and work packages are not always detailed and well described. For instance, it is not clear how the compounds to be tested will be selected, and, in general, the deliverables are quite vague and not exactly defined. The timetable is presented but it is more a summary than a punctual plan of the experimental protocol. The contingency plan is quite superficial. The possibility of networking is high, and high is the possibility to run for competitive and non-competitive funds.

Reviewer n. 2

This project aims to exploit 3D cellular models, to identify compounds of natural origin with pharmacological activity to cure MASH. The project is based on departmental collaborations, exploiting complementary expertise. Hepatic organoids can be challenging to develop, and this is the crucial step for the feasibility of the project, which otherwise will be limited to the extraction and preliminary evaluation of natural products. The presence of several collaborators makes it a good starting point to apply for further funding opportunity.

Reviewer n. 3

The proposal is a bit confounding for what concerns the objectives. While the title and some parts focus on the set up of a new method as the key objective, other parts of the proposal gave similar importance to compound identification for potential medical applications and industrial exploitation. This discrepancy in turn generates difficulties in view of defining the effective feasibility and in the risk evaluation. Apart from this, the proposal is scientifically interesting, particularly for what concerns the setup of a new method; on the other hands, I wonder why to use natural products and extracts instead of classical known small molecules as tools with an established physicochemical, pharmacological and pharmacokinetic profiles. This could allow to overcome the implicit risk in task 1 (not considered within the proposal) of failing with the selected compounds from natural sources. The proposal presents limited originality and some potential for innovation, but it should incorporate some more information on the existing competition, if any. Finally, the proposal is based on established departmental know-how and existing methodologies, and present some potential for further exploration and applications, even at the industrial level, in case of positive results.

Reviewer n. 4

The project results scientifically relevant since they will set up new spheroids mimicking MASH disease. The project is in line with the departmental know-how and the plan is feasible. Task 1 and 2 will be done by Prof. Dall'Acqua e Dott. Sut but are not reported the methodologies used to do that. Methodologies regarding their evaluation on MSC are well reported. The project reported numerous activities to be considered in two years. Indeed, the applicant also introduces metabolomic and lipidomic analysis. The setup of the new organoids could be challenging and taking more time during the project.

The contingency plan takes into consideration the task 3 that is the more challenging and it is also more interesting to be developed. The project could have perspective for collaborations and could have an industrial impact, since they plan to transfer the findings to companies devoted to the preparation of nutraceutical and also pharmaceutical products.

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 technical expertise of the applicant appears adequate and sufficient to supervise the project.

Reviewer n. 2

The PI has a good publication record and adequate expertise in the characterization of products form natural origin. She has the experience in pharmacology and she has participated in similar projects, and she possess the know-how to lead the research team and fulfil her part in the project.

Reviewer n. 3

The applicant has good competence and expertise to support the proposed project and to coordinate all the required activities. However, some question remains due to the critical points (see above) and the way the proposal is written.

Reviewer n. 4

The applicant has expertise in *in vivo* pharmacokinetic and toxicological studies and *in vivo* models of chronic liver diseases. Moreover, the applicant has expertise in biochemical assay and cell cultures in addition to enzymatic assays. The expertise is appropriate but not sufficient for task 1 and 2 that will be supplies by the other participant to the project with complementary experiences.

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 research team apparently brings together complementary expertise, although, besides professors, only one research fellow and for a short period is indicated.

Reviewer n. 2

The team is formed by several collaborators with complementary expertise, including an international partner. The presence of pharmacologist, medicinal chemist and oncologist guarantee the multidisciplinary know-how required.

Reviewer n. 3

the experience and competence of the team members are complementary and supportive for the project activity, including an external international collaboration.

Reviewer n. 4

Research team has complementary experiences. Overall the project need of experience in evaluating botanical products for the task 1 and 2 supplied by the other members. At the moment the project is not involved in international research collaborations.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2024

COMMISSIONE INTERNA

Project: Development of multicellular 3D in vitro models of metabolic dysfunction-associated steatohepatitis for the advanced screening of active natural compounds and extracts.
Applicant: Daniela Gabbia

Punti di forza

Il progetto presenta una solida base scientifica, con approcci innovativi e ben mirati verso la creazione di modelli preclinici avanzati e la valorizzazione di composti naturali per il trattamento della MASH.

Criticità

Lo sviluppo dei modelli proposti richiede una standardizzazione complessa e protocolli che non sempre sono stati descritti in maniera esaustiva. Proprio in relazione alla complessità tecnica dei modelli utilizzati, l'analisi dei rischi non appare adeguata. Non sempre risulta definito il ruolo di ciascun componente del progetto.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2024

COMMISSIONE ESTERNA

Project: G protein-coupled receptors roles in oligodendrocyte function
Applicant: Malfacini Davide

General assessment of scientific quality and innovation - Assessment of scientific plan

- *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? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate** and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives 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 project is, likely, significant and original but it is very confusing and hardly comprehensible as regards methods, materials, work packages, timeline and deliverables. Therefore, it is really difficult to evaluate it properly.

Reviewer n. 2
This project aims to describe GPCRs involvement in oligodendrocytes, opening up to possibly unexplored therapeutic options for multiple sclerosis. It develops in 3 objectives, and for each one the research methodology is clearly described. The plan seems feasible in the 2 years of the project. Risk analysis and contingency plans are contemplated for all the tasks. From this proposal is impossible to evaluate the involvement of the Department, as no research team is described.

Reviewer n. 3
A well written and organised proposal, scientifically significant, with a good level of both originality and innovation. The proposed activities are out of my direct experience, and I can hardly evaluate the feasibility within the given timelines; for sure a lot of work is considered, and this raises some concern from this point of view. One aspect that should have been discussed, at least in the introductory part, is why focussing on the GPCRs realm and not considering potential other targets, if any, described in the literature.

Reviewer n. 4
The project is scientifically significant and built with the departmental know-how but, in my opinion the project is not well written. Work packages and milestones are confusing and not correctly reported methodological procedures. Risk assessment and the contingency plan are not properly considered. The applicant only suggests to applied general alternatives methods. At the moment the project doesn't have international collaborations, applications, networking.

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
On the basis of the CV, the applicant apparently has the expertise presumably needed to supervise the project, but no specific indication of technical expertise is provided.

Reviewer n. 2
The PI has a postdoctoral experience in Italy and in Germany working on G protein coupled receptors. The experience is proven by publication on the topic, and the expertise of the applicant seems adequate to lead the project.

Reviewer n. 3
The applicant's skills are covering all the needs of the proposed project, and his international experience and connections would be an added value.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2024

Reviewer n. 4
The applicant reports that he is a pharmacologist with a focus on GPCR pharmacology and signaling but specific abilities are not reported.
The merits and expertise are sufficient to develop the project.

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
Only a PhD student is indicated as member of the research team, but no indication of the technical expertise is provided.

Reviewer n. 2
The team consists in one postdoc (with very limited contribution in months devoted to the project) and does not include international collaborations. Therefore, the lack of a proper team can be problematic for the adequate development of the project.

Reviewer n. 3
The team is adding to the project in terms of experience and competence, particularly in terms of know-how particularly for what concerns the bioinformatic side.

Reviewer n. 4
Research team comprises another person and the expertise seems the same of the applicant, therefore there is not complementarity. The project is not involved in international collaborations.

COMMISSIONE INTERNA

Project: G protein-coupled receptors roles in oligodendrocyte function
Applicant: Davide Malfacini

Punti di forza
Il progetto appare piuttosto originale. Le metodologie proposte sembrano essere sufficientemente innovative e in linea con gli expertise del proponente.

Criticità
Il progetto non è di facile interpretazione, ed alcuni aspetti risultano confusionari. Non è chiaro il ruolo dei collaboratori esterni. Inoltre, fa riferimento alla direttiva europea 2010/63/UE per la sperimentazione animale, ma mancano le specifiche e il codice del progetto approvato.

VALUTAZIONI PROGETTI DI RICERCA DI DIPARTIMENTO PRID-J – ANNO 2024

COMMISSIONE ESTERNA

Project: Nanomedicine-Driven Immunotherapeutic Strategies in Post-Operative Glioblastoma By Exploiting the STING Pathway
Applicant: Malfanti Alessio

General assessment of scientific quality and innovation - Assessment of scientific plan

- *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? Is the **plan realistically feasible**?*
- *Are the research **methods, materials, work packages, tasks, milestones and timeline appropriate** and in agreement with deliverables?*
- *Are the risk assessment and the contingency plan properly considered?*
- *This project has perspectives 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 project is, likely, significant and original but it is very confusing and hardly comprehensible as regards methods, materials, work packages, timeline and deliverables. Therefore, it is really difficult to evaluate it properly.

Reviewer n. 2
This is an ambitious project, that if successful will lead to breakthrough in the clinical management of brain cancer. Nevertheless, the project is ambitious to be realized in 2 years. It is unclear whether the resection model is already available at the host institution, and if there is an approved protocol (no animal work is declared in the proposal). The methodologies and workplan are not detailed. Also, who is going to perform the experiments, and all the related analysis is not detailed. Typically, this type of project would benefit from a multidisciplinary team and collaborators, the lack of which is one of the main drawbacks of this proposal.

Reviewer n. 3
The proposal is very interesting from a scientific standpoint, and maybe the abstract is a bit too concise, but some doubt is due from the organisational point of view. The project is highly ambitious and at high risk, as typical for innovative projects of high scientific value. All the tools and methodologies seem available, and the proposed activities may be feasible within the given timelines. On the other hands, according to the proposal, the applicant will work almost in isolation, and this raises some question due to the required multidisciplinary activities. The risk analysis is not complete, particularly for what concerns the T2. In case of positive results, the project may open to important future development and collaborations and in view of the medical need it would be appropriate an immediate enlargement of the team, particularly with a technological component.

Reviewer n. 4
The project is challenging, innovative and original. The plan is not easily feasible. It is not reported if the department has the know how to elaborate the project. Some experimental procedures are not completely clear. Risk assessment and the contingency plan were considered but some difficulties remain. The project has perspectives for international collaborations, applications and networking and also could has character of start-up research.

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

On the basis of the CV, the applicant apparently has the expertise presumably needed to supervise the project, but given the puzzling and disconcerting organization of the proposal, it is quite difficult to give a proper weight to his scientific skills and expertise.

Reviewer n. 2

There is no doubt that the PI has the knowledge to lead and perform both the technological and the biological experiments. His international profile and the multidisciplinary background guarantee the necessary expertise to coordinate such a project

Reviewer n. 3

The applicant has apparently a good experience and competence concerning most of the proficiencies required to support the proposed activities, but maybe such experiences are not all so thorough as required (eg the implications for in-vivo translation of the obtained results should be better expressed to properly design some in-vitro experiment).

Reviewer n. 4

The applicant developed strong and valuable expertise in the design of polymer-based nanomedicine as a potential solution for several untreatable cancers. The experiences could be appropriated and sufficient for the project.

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 proposal does not comprise a research team.

Reviewer n. 2

Throughout the proposal there is no indication on team members (doctoral students, postdocs etc) nor international collaborators who can assist the PI in the fulfilment of the project. Also, for the PI no time commitment is added. Therefore, this aspect is impossible to evaluate.

Reviewer n. 3

It does not exist

Reviewer n. 4

There are no other members in the research team. The project is not involved in international collaboration at the moment.

COMMISSIONE INTERNA

Project: Nanomedicine-Driven Immunotherapeutic Strategies in Post-Operative Glioblastoma By Exploiting the STING Pathway

Applicant: Alessio Malfanti

Punti di forza

Il progetto è originale ed interessante, anche se frammentario. La tematica affrontata è di grande rilevanza scientifica.

Criticità

L'aspetto più critico riguarda la totale assenza di un gruppo di ricerca. Il proponente infatti presenta un progetto non di facile realizzazione e non menziona collaboratori interni o esterni al dipartimento dove verrà svolta la ricerca. Inoltre, ci sono molti spunti di proposta di attività non ben amalgamati.